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(71) Applicants (for all designated States except US): SAGAMI CHEMICAL RESEARCH CENTER [JP/JP]; 4-1, Nishi-Ohnuma 4-chome, Sagamihara-shi, Kanagawa 229-0012 (JP). PROTEGENE INC. [JP/JP]; 2-20-3, Naka-cho, Meguro-ku, Tokyo 153-0065 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): KATO, Seishi [JP/JP]; 3-46-50, Wakamatsu, Sagamihara-shi, Kanagawa 229-0014 (JP). KIMURA, Tomoko [JP/JP]; 715, 2-9-1, Kohoku, Tsuchiura-shi, Ibaraki 300-0032 (JP).

(74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).

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(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

(57) Abstract: The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells expressing these DNAs and antibodies directed to these proteins.

#### DESCRIPTION

# Human Proteins Having Hydrophobic Domains and DNAs Encoding These Proteins

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#### TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, eukaryotic 10 expressing these DNAs and antibodies directed to these proteins. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies directed to these proteins. The human cDNAs of the present invention can be utilized as probes for genetic diagnosis and gene sources for gene therapy. Furthermore, 15 the cDNAs can be utilized as gene sources for producing the proteins encoded by these cDNAs in large quantities. Cells into which these genes are introduced to express secretory proteins or membrane proteins in large quantities can be utilized for detection of the corresponding receptors or 20 ligands, screening of novel small molecule pharmaceuticals and the like. The antibodies of the present invention can be utilized for the detection, quantification, purification and the like of the proteins of the present invention.

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## BACKGROUND ART

Cells secrete many proteins extracellularly. These secretory proteins play important roles in the proliferation differentiation induction, the control, the transport, the biophylaxis, and the like of the cells. Unlike intracellular proteins, the secretory proteins exert their actions outside the cells. Therefore, they can be administered in the intracorporeal manner such as the so that they possess hidden injection or the drip, potentialities as pharmaceuticals. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents and the like addition, pharmaceuticals. In currently employed as secretory proteins other than those described above are undergoing clinical trials for developing their use as pharmaceuticals. It is believed that the human cells produce many unknown secretory proteins. Availability of these secretory proteins as well as genes encoding them expected to lead to development of novel pharmaceuticals utilizing them.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters and the like in the material transport and the signal transduction through the cell membrane. Examples thereof include receptors for various cytokines, ion

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channels for the sodium ion, the potassium ion, the chloride ion and the like, transporters for saccharides and amino acids and the like. The genes for many of them have already been cloned. It has been clarified that abnormalities in these membrane proteins are involved in a number of previously cryptogenic diseases. Therefore, discovery of a new membrane protein is expected to lead to elucidation of the causes of many diseases, so that isolation of new genes encoding the membrane proteins has been desired.

10 Heretofore, due to difficulty in the purification from human cells, many of these secretory proteins and membrane proteins have been isolated by genetic approaches. A general method is the so-called expression cloning method, in which a cDNA library is introduced into eukaryotic cells to express cDNAs, and the cells secreting, or expressing on the surface of membrane, the protein having the activity of interest are then screened. However, only genes for proteins with known functions can be cloned by using this method.

In general, a secretory protein or a membrane protein possesses at least one hydrophobic domain within the 20 protein. After synthesis on ribosomes, such domain works as a secretory signal or remains in the phospholipid membrane to be entrapped in the membrane. Accordingly, existence of a highly hydrophobic domain is observed in the amino acid sequence of a protein encoded by a cDNA when the 25

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whole base sequence of the full-length cDNA is determined, it is considered that the cDNA encodes a secretory protein or a membrane protein.

# 5 OBJECTS OF INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells that are capable of expressing these DNAs and antibodies directed to these proteins. This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

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# SUMMARY OF INVENTION

As the result of intensive studies, the present inventors have successfully cloned cDNAs encoding proteins having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. Thus, the present invention provides a human protein having hydrophobic domain(s), namely a protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130. Moreover, the present invention provides a DNA

encoding said protein, exemplified by a cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131 to 150, an expression vector that is capable of expressing said DNA by in vitro translation or in eukaryotic cells, a transformed eukaryotic cell that is capable of expressing said DNA and of producing said protein and an antibody directed to said protein.

# 10 BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03171.

ig. 2 illustrates the

hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03424.

Fig. 3 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03444.

Fig. 4 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03478.

Fig. 5 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03499.

	Fig.	6	illustrates	the
	hydrophobicity/hydroph	ilicity pro	ofile of the protein en	coded
	by clone HP03500.			
	Fig.	7	illustrates	the
5			ofile of the protein er	coded
J	by clone HP10691.			
	Fig.	8	illustrates	the
	hydrophobicity/hydroph	nilicity pr	ofile of the protein e	ncoded
	by clone HP10703.			
10	Fig.	9	illustrates	- the
	hydrophobicity/hydroph	nilicity p	cofile of the protein e	ncoded
			2.2	
	Fig.	10	illustrates	the
	hydrophobicity/hydrop	hilicity p	rofile of the protein $\epsilon$	encoded
15	by clone HP10712.			
	Fig.	11	illustrates	
	hydrophobicity/hydrop	hilicity p	rofile of the protein o	encoded
	by clone HP03010.		: · · · · · · · · · · · · · · · · · · ·	
	Fig.	12	illustrates	
20	hydrophobicity/hydrop	philicity I	profile of the protein	encoded
	by clone HP03576.	. · · · · · · · · · · · · · · · · · · ·		
	Fig.	13	illustrates	
	hydrophobicity/hydro	philicity	profile of the protein	encoded
	by clone HP03611.			
25	Fig.	14	illustrates	: the

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hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03612.

Fig. 15 illustrates hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10407.

Fig. 16 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10713.

illustrates

the hydrophobicity/hydrophilicity profile of the protein encoded 10 by clone HP10714.

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Fig.

Fig. 18 illustrates hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10716.

15 Fig. 19 illustrates hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10717.

Fig. 20 illustrates . the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10718.

Fig. 21 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03745.

Fig. 22 illustrates . the 25 hydrophobicity/hydrophilicity profile of the protein encoded

the

by clone HP03747.

illustrates 🚟 23 Fig. hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10719.

illustrates the 24 Fig. 5 hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10720.

illustrates ' the 25 Fig. hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10721. 10

the illustrates 26 Fig. hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10725.

illustrates 27 Fig. hydrophobicity/hydrophilicity profile of the protein encoded 15 . . by clone HP10727.

the illustrates 28 Fig. hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10728.

29 illustrates Fig. 20 hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10730.

the illustrates 30 Fig. hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10742.

	•	Fig.	31	ill	ustra	tes .	the
		hydrophobicity/hydrophil	icity	profile of	the	protein	encoded
	•	by clone HP03800.			•		
		Fig.	32	ill	ıstrai	tes .	the
	5	hydrophobicity/hydrophil	icity	profile of	the	protein	encoded
		by clone HP03831.					
		Fig.	33	illu	ıstrat	ces	the
		hydrophobicity/hydrophil	icity	profile of	the	protein	encoded
	•	by clone HP03879.					
	10	Fig.	34	illu	strat	es	the
		hydrophobicity/hydrophil	icity	profile of	the	protein	encoded
		by clone HP03880.					
		Fig.	35	illu	strat	.es	the
		hydrophobicity/hydrophil:	icity p	profile of	the	protein	encoded
	15	by clone HP10704.					:
		Fig.	36	illu	strat	es	the
		hydrophobicity/hydrophili	icity p	profile of	the	protein	encoded
		by clone HP10715.					
		Fig.	37	illu	strat	es	the
	20	hydrophobicity/hydrophili	city p	profile of	the ;	protein	encoded
		by clone HP10724.	-				
		Fig.	38	illu	strate	es <sub>.</sub>	the
		hydrophobicity/hydrophili	city p	profile of	the p	protein	encoded
		by clone HP10733.					
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	hydrophobicity/hydrophili	city	profile	of th	e prote	ein e	encodeo	ţ
	by clone HP10734.	• •						
	Fig.	10	i	llustr	ates	-	the	9
	hydrophobicity/hydrophili	city	profile	of th	e prot	ein (	encode	£
5	by clone HP10756.				•		:	
	Fig.	41	i	llustr	ates		th	e
	hydrophobicity/hydrophili	city	profile	of th	e prot	ein.	encode	d
	by clone HP03670.			•		÷		
	Fig.	42	i	llustr	rates		th	е
10	hydrophobicity/hydrophil:	city	profile	of th	ne prot	ein	encode	d
	by clone HP03688.				·		A.	
	Fig.	43	· i	llust	rates	•	th	e
	hydrophobicity/hydrophil	city	profile	of th	ne prot	ein	encode	:d
	by clone HP03825						*	
15	Fig.	44	. i	illust	rates		: th	ıe
	hydrophobicity/hydrophil	icity	profile	of the	he prot	tein	encode	ed.
.,	by clone HP03877.							
	Fig.	45	. :	illust	rates		tì	ıe
	hydrophobicity/hydrophil	icity	profile	of t	he pro	tein	encode	∍d
20	by clone HP10765.	• 0						
	Fig.	46		illust	rates		tl	he
	hydrophobicity/hydrophil	icity	y profile	of t	he pro	tein	encode	ed
	by clone HP10766.			•		•		
	Fig.							he
25	hydrophobicity/hydrophil	icit	y profile	e of t	he pro	tein	encod	ed

by clone HP10770.

Fig. 48 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10772.

Fig. 49 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10773.

Fig. 50 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10776.

## DETAILED DESCRIPTION OF THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolating proteins 15 from human organs, cell lines or the like, a method for preparing peptides by the chemical synthesis based on the amino acid sequences of the present invention, or a method for producing proteins by the recombinant DNA technology using the DNAs encoding the hydrophobic domains of the 20 present invention. Among these, the method for producing proteins by the recombinant DNA technology is preferably employed. For example, the proteins can be expressed in vitro by preparing an RNA by in vitro transcription from a vector having the cDNA of the present invention, and then carrying out in vitro translation using this RNA as a 25

region into a suitable expression vector by the method known in the art may lead to expression of a large amount of the encoded protein in prokaryotic cells such as Escherichia coli, Bacillus subtilis, etc., and eukaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case where the protein of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro by incorporating the translated region of this cDNA into a vector having an RNA polymerase promoter, and then adding the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a wheat germ extract, which contains an RNA polymerase corresponding to promoter. The RNA polymerase promoters are exemplified by T7, T3, SP6 and the like. The vectors containing promoters for these RNA polymerases are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II and the like. Furthermore, the protein of the present invention can be expressed in the secreted form or the form incorporated in the microsome membrane when a canine pancreas microsome or the like is added to the reaction system.

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In the case where the protein of the present invention is produced by expressing the DNA in a microorganism such as Escherichia coli etc., a recombinant

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expression vector in which the translated region of the cDNA of the present invention is incorporated into an expression vector having an origin which is capable of replicating in the microorganism, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator and the like is constructed. After transformation of the host cells with this expression vector, the resulting transformant is cultivated, whereby the protein encoded by the cDNA can be produced in large quantities in the microorganism. In this case, a protein fragment containing any translated region can be obtained by adding an initiation codon and a termination codon in front of and behind the selected translated region to express the protein. Alternatively, the protein can be expressed as a fusion protein with another protein. Only the portion of the protein encoded by the cDNA can be obtained by cleaving this fusion protein with a suitable protease. The expression vectors for Escherichia coli are exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system and the like.

In the case where the protein of the present invention is produced by expressing the DNA in eukaryotic cells, the protein of the present invention can be produced as a secretory protein, or as a membrane protein on the surface of cell membrane, by incorporating the translated region of the cDNA into an expression vector for eukaryotic

cells that has a promoter, a splicing region, a poly(A) addition site and the like, and then introducing the vector into the eukaryotic cells. The expression vectors are exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vectors, pRS, pYES2 and the like. Examples of eukaryotic cells to be used in general include mammalian cultured cells such as monkey kidney COS7 cells, Chinese hamster ovary CHO cells and the like, budding yeasts, fission yeasts, silkworm cells, Xenopus oocytes and the like. Any eukaryotic cells may be used as long as they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eukaryotic cells by using a method known in the art such as the electroporation method, the calcium phosphate method, the liposome method, the DEAE-dextran method and the like.

After the protein of the present invention is expressed in prokaryotic cells or eukaryotic cells, the protein of interest can be isolated and purified from the culture by a combination of separation procedures known in the art. Examples of the separation procedures include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or centrifugation, dialysis, solvent precipitation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric 25 focusing, ion-exchange chromatography, hydrophobic

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chromatography, affinity chromatography, reverse phase chromatography and the like.

The proteins of the present invention also include peptide fragments (of 5 amino acid residues or containing any partial amino acid sequences in the amino acid sequences represented by SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130. These peptide fragments can be utilized as antigens for preparation of antibodies. Among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the protein of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal sequence [JP-A 8-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secreted forms. Such proteins or peptides in the secreted forms shall also come within the scope of the protein of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences of the proteins, expression of the proteins in appropriate eukaryotic cells affords the proteins to which sugar chains are added. Accordingly, such proteins or peptides to which sugar chains are added shall also come

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within the scope of the protein of the present invention.

The DNAs of the present invention include all the DNAs encoding the above-mentioned proteins. These DNAs can be obtained by using a method for chemical synthesis, a method for cDNA cloning and the like.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries derived from the human cells. The cDNAs are synthesized by using poly(A)\* RNAs extracted from human cells as templates. The human cells may be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be synthesized by using any method such as the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-(1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J., Gene 25: 263-269 (1983)] and the like. However, it is desirable to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available human cDNA libraries can be utilized. The cDNAs of the present invention can be libraries by synthesizing CDNA from the cloned oligonucleotide on the basis of base sequences of any portion in the cDNA of the present invention and screening the cDNA libraries using this oligonucleotide as a probe for colony or plaque hybridization according to a method known in the art. In addition, the cDNA fragments of the present invention can be prepared from an mRNA isolated from human cells by the RT-PCR method in which oligonucleotides which hybridize with both termini of the cDNA fragment of interest are synthesized, which oligonucleotides are then used as the primers.

The CDNAs of the present invention characterized in that they comprise any one of the base sequences represented by SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110 and 131 to 140 or the base sequences 10 represented by SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120 and 141 to 150. Tables 1 and 2 summarizes the clone number (HP number), the cell from which the cDNA clone was obtained, the total number of bases of the cDNA, and the number of the amino acid residues of the encoded protein, 15 for each of the cDNAs.

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Table 1

Table		<del></del>				Number
			HP		Number	of amino
SEQ	ID N	0	number	Cell	of	acid
* -					bases	residues
1,	11,	21	HP03171	Thymus	2042	267
2,	12,	22	HP03424	Liver	1433	419
3,	13,	23	HP03444	Kidney	. 1917 .	415
4,	14,	24	HP03478	Umbilical cord blood	2258	380
5,	15,	25	HP03499	Kidney	1973	585
6, <sup>.</sup>	16,	26	HP03500	kidney	1606	331
7,	17,	27	HP10691	Umbilical cord blood	2380	345
8,	18,	28	HP10703	Kidney	2017	89
9,	19,	29	HP10711	Kidney	1606	406
10,	20,	30	HP10712	Kidney	1695	192
31,	41,	51	HP03010	Kidney	1551	377
32,	42,	52	HP03576	Kidney	1713	81
33,	43,	53	·HP03611	Kidney	1758	487
34,	44,	54	HP03612	Kidney	1550	375
35,	45,	55	HP10407	Stomach cancer	1485	350
36,	46,	56	HP10713	Kidney	2694	667
37,	47,	57	HP10714	Umbilical cord blood	3297	464
38,	48,	58	HP10716	Umbilical cord blood	2126	470
39,	49,	59	HP10717	Kidney	1781	243
40,	50,	60	HP10718	Umbilical cord blood	1788	270
61,	71,	81	HP03745	Kidney	1376	389
62,	72,	82	HP03747	Umbilical cord blood	2392	348
63,	73,	83	HP10719	Kidney	1416	261
64,	74,	84	HP10720	Kidney	1347	222
65,	75,	85	HP10721	Kidney	2284	183

Table 2

SEQ I	D NO	0	HP number	Cell	Number of bases	Number of amino acid residues
66, 7	6,	86	HP10725	Kidney	1737	262
67, 7	7,	87	HP10727	Umbilical cord blood	1556	168
68, 7	8,	88	HP10728	Umbilical cord blood	1855	243
69, 7	9,	89	HP10730	Umbilical cord blood	2530	428
70, 8	Ο,	90	HP10742	Umbilical cord blood	1911	283
91, 10	1, :	111	HP03800	Umbilical cord blood :	1633	476
92, 10	2, :	112	HP03831	Kidney	1095	226
93, 10	3, :	113	HP03879	Kidney	1602	305
94, 10	4, :	114	HP03880	Kidney	897	227
. 95, 10	5, :	115	HP10704	Kidney	1866	441
96, 10	6, :	116	HP10715	Umbilical cord blood	2198	265
97, 10	7, :	117	HP10724	Umbilical cord blood	2180	208
98, 10	8, 3	118	HP10733	Umbilical cord blood	1527	400
99, 10	9, :	119	HP10734	Umbilical cord blood	1905	192
100, 11	0, 3	120	HP10756	Kidney	998	260
121, 13	1, :	141	HP03670	Umbilical cord blood	1622	337
122, 13	2, 3	142	HP03688	Umbilical cord blood	2475	236
123, 13	3, :	143	HP03825	Kidney	1739	560
124, 13	4,	144	HP03877	Kidney	2005	406
125, 13	5, :	145	HP10765	Umbilical cord blood	1558	453
126, 13	6, 3	146	HP10766	Kidney	1005	59
127, 13	7,	147	HP10770	Kidney	969	210
128, 13	8,	148	HP10772	Kidney	1241	165
129, 13	9,	149	HP10773	Kidney	1174	162
130, 14	0,	150	HP10776	Kidney	1012	221

The same clones as the cDNAs of the present invention can be easily obtained by screening the cDNA libraries constructed from the human cell lines or human

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tissues utilized in the present invention using an oligonucleotide probe synthesized on the basis of the base sequence of the cDNA provided in any one of SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131 to 150.

In general, the polymorphism due to the individual differences is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are added, deleted and/or substituted with other nucleotides in SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131 to 150 shall come within the scope of the present invention.

Similarly, any protein in which one or plural amino acids are added, deleted and/or substituted with other amino acids resulting from the above-mentioned changes shall come within the scope of the present invention, as long as the protein possesses the activity of the protein having any one of the amino acid sequences represented by SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130.

The cDNAs of the present invention also include cDNA fragments (of 10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110 and 131 to 140 or in the base sequences represented by SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120 and 141 to 150. Also, DNA fragments consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can

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be utilized as the probes for the genetic diagnosis.

The antibody of the present invention can be obtained from a serum after immunizing an animal using the protein of the present invention as an antigen. A peptide that is chemically synthesized based on the amino acid sequence of the present invention and a protein expressed in eukaryotic or prokaryotic cells can be used as an antigen. Alternatively, an antibody can be prepared by introducing the above-mentioned expression vector for eukaryotic cells into the muscle or the skin of an animal by injection or by using a gene gun and then collecting a serum therefrom (JP-A 7-313187). Animals that can be used include a mouse, a rat, a rabbit, a goat, a chicken and the like. A monoclonal antibody directed to the protein of the present invention can be produced by fusing B cells collected from the spleen of the immunized animal with myelomas to generate hybridomas.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for

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introduction of DNA).

## Research Uses and Utilities

The polynucleotides provided by the invention can be used by the research community for various The polynucleotides can be used to express purposes. for analysis, characterization recombinant protein therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either at a particular stage of constitutively or differentiation or development or in disease states); "as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA patients to identify potential sequences in disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein

(such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris t al., Cell '75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-10 throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding 15 protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can 20 be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or 2.5 agonists of the binding interaction. .:..

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Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

#### Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation

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#### Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 25 137:3494-3500, 1986; Bertagnolli et al., J. Immunol.

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145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

- Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.
- Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology.

  J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. J.E.e.a.

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Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 -Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

25 Immune Stimulating or Suppressing Activity

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A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania malaria spp. and various fungal infections such candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune

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pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. immune suppression is desired in . which conditions, (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an may progress or response already in immune immune response. induction of an preventing the inhibited by functions of activated T cells may be inducing specific suppressing T cell responses or by tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigenspecific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by

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the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. tissue transplants, rejection of Typically, in transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the cells without transmitting the corresponding immune costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant.

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Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases.

Many autoimmune disorders are the result of inappropriate

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activation of T cells that are reactive against self tissue and which promote the production of cytokines autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor: ligand interactions of B lymphocyte antiqens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents induce antigen-specific tolerance of may autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can ... be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy.

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Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte

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antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having-B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a

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cytoplasmic-domain truncated portion) of an MHC class I lphachain protein and  $\beta$  , microglobulin protein or an MHC class II  $\alpha$  chain protein and an MHC class II eta chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated invariant chain, can such as the protein, cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19;

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Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Thl and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E.

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Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-In Vitro assays for Interscience (Chapter 3, Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 20 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

## Hematopoiesis Regulating Activity

in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or

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erythroid cells; in supporting the growth and proliferation granulocytes cells such as myeloid (i.e., traditional CSF activity) monocytes/macrophages useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting megakaryocytes proliferation of and growth the consequently of platelets thereby allowing prevention or disorders such various platelet treatment of thrombocytopenia, and generally for use in place of or complementary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the abovementioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without and paroxysmal nocturnal aplastic anemia limitation, hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or marrow conjunction with bone (i.e.. ex-vivo in progenitor cell transplantation or with peripheral as normal transplantation (homologous or heterologous)) cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

25. Suitable assays: for proliferation and

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differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

10 Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. 15 Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. 20 Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New 25 York, NY. 1994; Long term bone marrow cultures in the

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presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

### Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth

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repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or

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ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, differentiation of progenitors of tendonligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be in the treatment of tendinitis, carpal tunnel useful The defects. syndrome and other tendon ligament or compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be cells and for proliferation of neural for useful regeneration of nerve and brain tissue, i.e. for treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nerve injuries, system, such as peripheral nervous peripheral neuropathy and localized neuropathies, central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic

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lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

25 A protein of the present invention may also be

useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. W095/16035 (bone, cartilage, tendon); International Patent Publication No. W095/05846 (nerve, neuronal); International Patent Publication No. W091/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

#### Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of

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follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin  $\alpha$  family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- $\beta$  group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572; 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et

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al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

## Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, and/or endothelial epithelial eosinophils, Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized For example, attraction of lymphocytes, infections. monocytes or neutrophils to tumors or sites of infection may 15 result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell

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chemotaxis.

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The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

### Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other

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hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke)).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

### Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen

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presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

#### Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity

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may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cellcell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the promoting inhibiting or inflammatory process, extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, rejection, nephritis, complement-mediated hyperacute cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

#### Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly

(such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

# Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body example, breast size or shape (such as, for part augmentation or diminution, change in bone form or shape); effecting biorhythms or cardiac cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or

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nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders), and violent behaviors: providing analgesic effects or other reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulinlike activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

### Examples

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in more detail by the following Examples, but Examples are not intended to restrict the present invention. The basic procedures with regard to the recombinant DNA and the enzymatic reactions were carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold

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Spring Harbor Laboratory, 1989]. Unless otherwise stated, restriction enzymes and various modifying enzymes to be used were those available from Takara Shuzo. The buffer compositions and the reaction conditions for each of the enzyme reactions were as described in the attached instructions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Selection of cDNAs Encoding Proteins Having

10 Hydrophobic Domains

Human liver cDNA library (WO 98/21328) and human stomach cancer cDNA library (WO 98/21328), as well as the cDNA libraries constructed from human kidney mRNA (Clontech), human thymus mRNA (Clontech) and human umbilical cord blood mRNA were used as cDNA libraries.

Full-length cDNA clones were selected from the respective libraries and the whole base sequences thereof were determined to construct a homo-protein cDNA bank consisting of the full-length cDNA clones. The hydrophobicity/hydrophilicity profiles were determined for the proteins encoded by the full-length cDNA clones registered in the homo-protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic domain. A clone that has a hydrophobic region

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being assumed as a secretory signal or a transmembrane domain in the amino acid sequence of the encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a  $T_NT$  rabbit reticulocyte lysate kit (Promega). In this case, [35S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was subjected to the reaction at 30°C for 90 minutes in the reaction solution of a total volume of 25 µl containing 12.5 µl µ of TNT rabbit reticulocyte lysate, 0.5 µl of a buffer solution (attached to the kit), 2 µl of an amino acid mixture (without methionine), 2  $\mu$ l of [35S]methionine (Amersham) (0.37 MBq/ $\mu$ l), 0.5 µl of T7 RNA polymerase, and 20 U of RNasin. experiment in the presence of a membrane system was carried out by adding 2.5 µl of a canine pancreas microsome fraction (Promega) to the reaction system. To 3 µl of the reaction solution was added 2 µl of the SDS sampling buffer (125 mM Tris-hydrochloride buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis.

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The molecular weight of the translation product was determined by carrying out the autoradiography.

## (3) Expression in COS7

Escherichia coli cells harboring the expression vector for the protein of the present invention were cultured at 37°C for 2 hours in 2 ml of the 2 x YT culture medium containing 100  $\mu$ g/ml of ampicillin, the helper phage M13K07 (50  $\mu$  1) was added thereto, and the cells were then cultured at 37°C overnight. Single-stranded phage particles were obtained by polyethylene glycol precipitation from a supernatant separated by centrifugation. The particles were suspended in 100  $\mu$ l of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The cultured cells derived from monkey kidney, COS7, were cultured at 37°C in the presence of 5% CO<sub>2</sub> in the Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum. 1 x 10<sup>5</sup> COS7 cells were inoculated into a 6-well plate (Nunc, well diameter: 3 cm) and cultured at 37°C for 22 hours in the presence of 5% CO<sub>2</sub>. After the medium was removed, the cell surface was washed with a phosphate buffer solution followed by DMEM containing 50 mM Trishydrochloride (pH 7.5) (TDMEM). A suspension containing 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM medium and 3 µl of TRANSFECTAM<sup>TM</sup> (IBF) was added to the cells and the cells were cultured at 37°C for 3 hours in the presence of 5% CO<sub>2</sub>. After the sample solution was removed,

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the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf serum was added, and the cells were cultured at 37°C for 2 days in the presence of 5% CO<sub>2</sub>. After the medium was exchanged for a medium containing [35S]cysteine or [35S]methionine, the cells were cultured for one hour. After the medium and the cells were separated each other by centrifugation, proteins in the medium fraction and the cell membrane fraction were subjected to SDS-PAGE.

#### (4) Preparation of Antibodies

A plasmid vector containing the cDNA of the present invention was dissolved in a phosphate buffer solution (PBS: 145 mM NaCl, 2.68 mM KCl, 8.09 mM Na2HPO4, 2 mM  $KH_2PO_4$ , pH 7.2) to a concentration of 2  $\mu g/\mu l$ . 25  $\mu l$  each (a total of 50 µl) of the thus-prepared plasmid solution in PBS was injected into the right and left musculi quadriceps femoris of three mice (ICR line) using a 26 guage needle. After similar injections were repeated for one month at intervals of one week, blood was collected. The collected blood was stored at 4°C overnight to coagulate the blood, and then centrifuged at 8,000 x g for five minutes to obtain a supernatant. NaN, was added to the supernatant to a concentration of 0.01% and the mixture was then stored at 4°C. The generation of an antibody was confirmed immunostaining of COS7 cells into which the corresponding vector had been introduced or by Western blotting using a

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cell lysate or a secreted product.

(5) Clone Examples

<HP03171> (SEQ ID NOS: 1, 11 and 21)

Determination of the whole base sequence of the cDNA insert of clone HP03171 obtained from cDNA library of human thymus revealed the structure consisting of a 90-bp 5'-untranslated region, a 804-bp ORF, and a 1148-bp 3'untranslated region. The ORF encodes a protein consisting of 267 amino acid residues and there existed one putative transmembrane domain. Figure 1 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyteof the present protein. In vitro Doolittle method, translation resulted in formation of a translation product of 34 kDa that was somewhat larger than the molecular weight of 30,234 predicted from the ORF. In this case, The addition of a microsome led to the formation of a product of 38 kDa. In addition, there exists in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Thr-Thr at position 169).

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to chicken putative transmembrane protein E3-16 (Accession No. AAB70816). Table 3 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and chicken putative

transmembrane protein E3-16 (GG). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 43.0% in the entire region.

Table 3

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غور دومه محافظ الرابي والمستعدد الرابان

HP RATRRINKRGAKNCNAIRHFENTFVVETLICGVV

\* \*\* \* \*\* \* \*\*\* \* \*\*\*\*

GG KEAMKGIQKREAVNCRKIRHFENRFAMETLICEQ

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AL036384) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP03424> (SEQ ID NOS: 2, 12 and 22)

Determination of the whole base sequence of the cDNA insert of clone HP03424 obtained from cDNA library of human liver revealed the structure consisting of a 4-bp 5'-untranslated region, a 1260-bp ORF, and a 169-bp 3'-untranslated region. The ORF encodes a protein consisting of 419 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 50 kDa that was somewhat larger than the molecular weight

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of 46,375 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 54 kDa. In addition, there exist in the amino acid sequence of this protein six sites at which N-glycosylation may occur (Asn-Ala-Ser at position 29, Asn-Val-Thr at position 40, Asn-Cys-Thr at position 112, Asn-Lys-Ser at position 135, Asn-Ile-Ser at position 172 and Asn-Phe-Ser at position 189). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from aspartic acid at position 28.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Drosophila melanogaster GOLIATH protein (Accession No. Q06003). Table 4 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Drosophila melanogaster GOLIATH protein (DM). Therein, the marks of -, \*, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 40.8% in the intermediate region of 218 amino acid residues.

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	Table 4	
	, , , , , , , , , , , , , , , , , , ,	<del>-</del>
	HP MSCAGRAGPARLAALALLTCSLWPARADNASQEYYTALINVTVQEPGRGAPLTFRIDRGR	
5	HP YGLDSPKAEVRGQVLAPLPLHGVADHLGCDPQTRFFVPPNIKQWIALLQRGNCTFKEKIS	:
	HP RAAFHNAVAVVIYNNKSKEEPVTMTHPGTGDIIAVMITELRGKDILSYLEKNISVQMTIA	
	* ** *.*. *.*	
	DM MQLEKMQIKGKTRNIAAVITYQNIGQDLSLTLDKGYNVTISII	
10		. (2*,
	HP VGTRMPPKNFSRGSLVFVSISFIVLMIISSAWLIFYFIQKIRYTNARDRNQRRLGDAA	
	* * * * .****** * * ***** ** . * * . * . * . *	
	DM EGRRGVRTISSLNRTSVLFVSISFIVDDILCWLIFYYIQRFRYMQAKDQQSRNLCSVT	٠
15	HP KKAISKLTTRTVKKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEH	n:
	**** *. * * * * * * * * * * * * * * * *	
	DM KKAIMKIPTKTGKFSD-EKDLDSDCCAICIEAYKPTDTIRILPCKHEFHKNCIDPWLIEH	
	HP CTCPMCKLNILKALGIVPNLPCTDNVAFDMERLTRTQAVNRRSALGDLAGDNSLGLEPLR	
20	******* * * *	347
	DM RTCPMCKLDVLKFYGYVVGDQIYQTPSPQHTAPIASIEEVPVIVVAVPHGPQPLQPLQ	
	e in the second of the second	
	HP TSGISPLPQDGELTPRTGEINIAVTKEWFIIASFGLLSALTLCYMIIRATASLNANEVEW	
	.**	
25	DM ASNMSSFAPSHYFQSSRSPSSSVQQQLAPLTYQPHPQQAASERGRRNSAPATMPHAITAS	= <u>C</u>

HP F

DM HQVTDV

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA082118) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03444> (SEQ ID NOS: 3, 13 and 23)

15 Determination of the whole base sequence of the cDNA insert of clone HP03444 obtained from cDNA library of human kidney revealed the structure consisting of a 209-bp 5'-untranslated region, a 1248-bp ORF, and a 460-bp 3'untranslated region. The ORF encodes a protein consisting of 20 415 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 43 kDa that was somewhat smaller than the molecular 25

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weight of 45,691 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 42 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glutamine at position 24.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human type I procollagen C-proteinase enhancer protein (Accession No. BAA23281). Table 5 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human type I procollagen C-proteinase enhancer protein (CP). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 43.6% in the entire region.

20 Table 5

HP MRGANAWAPLCLLLAAATQLSRQQSPERPVFTCGGILTGESGFIGSEGFPGVYP

\* \*\*. \* \* . . . . \*\*\*\* \*\*\* . . \*\*\*\*\*. . \*\*

CP MLPAATASLLGPLLTACALLPFA-Q-GQTPNYTRPVFLCGGDVKGESGYVASEGFPNLYP

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	HP PNSKCTWKITVPEGKVVVLNFRFIDLESDNLCRYDFVDVYNGH-ANGQRIGRFCGTFRPG
	**. * * ****** * * * * * * * * * * * *
	CP PNKECIWTITVPEGQTVSLSFRVFDLELHPACRYDALEVFAGSGTSGQRLGRFCGTFRPA
-	HP ALVSSGNKMMVQMISDANTAGNGFMAMFSAAEPNERGDQYCGGLLDRPSGSFKTPNWPDR
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	. **. ** * * *
	CP PLVAPGNQVTLRMTTDEGTGGRGFLLWYSGRATSGTEHQFCGGRLEKAQGTLTTPNWPES
	HP DYPAGVTCVWHIVAPKNQLIELKFEKFDVERDNYCRYDYVAVFNGGEVNDARRIGKYCGD
10	***, *, * ***, ** , *, *, *, *****, *, *
	CP DYPPGISCSWHIIAPPDQVIALTFEKFDLEPDTYCRYDSVSVFNGAVSDDSRRLGKFCGD
	HP SPPAPIVSERNELLIQFLSDLSLTADGFIGHYIFRPKKLPTTTE
	· *. * ** **** **. **** · * *
15	CP AVPGSISSEGNELLVQFVSDLSVTADGFSASYKTLPRGTAKEGQGPGPKRGTEPKVKLPP
	HP QPVTTTFPVTTGLKTTVALCQQKCRRTGTLEGNYCSSDFVLAGTVITTITRDG-SLHATV
	CP KSQPPEKTEESPSAPDAPTCPKQCRRTGTLQSNFCASSLVVTATVKSMVREPGEGLAVTV
20 .	
	HP SIINIYKEGNLAIQQAGKNMSARLTVVCKQCPLLRRGLNYIIMGQVGEDGRGKIM-PNSF
	*. *. **. *
	CP SLIGAYKTGGLDLPSPPTGASLKFYVPCKQCPPMKKGVSYLLMGQV-EENRGPVLPPESF
25-	HP IMMFKTKNQKLLDALKNKQC

## CP VVLHRPNQDQILTNLSKRKCPSQPVRAAASQD

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. D78874) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

### <HP03478> (SEQ ID NOS: 4, 14 and 24)

Determination of the whole base sequence of the cDNA insert of clone HP03478 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 224-bp 5'-untranslated region, a 1143-bp ORF, and a 891-bp 3'-untranslated region. The ORF encodes a protein consisting of 380 amino acid residues and there existed five putative transmembrane domains. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the

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protein was similar to Halocynthia roretzi HrPET-1 protein (Accession No. BAA81907). Table 6 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Halocynthia roretzi HrPET-1 protein (HR). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 36.8% in the entire region.

Table 6

HP MLQTLYDYFWWERLWLPVNLTWADLEDRDGRVYAKASDLYITLPLALLFLIVRYFFEL 15 HR MDLLMDLYHWFWNEKFWLPQNLTWEDLKRTEEKQFGETRDLWLTFPLCITVLCIRFSVEK HP YVATPLAALLNIKEKTRLRAPPNATLEHFYLTSGKQPKQVEVELLSRQSGLSGRQVERWF HR GIARPLGKWLNLSERLHTPPRENIVLEKVYKTITRKPNYSQVEDLCKQTGWRKHEINVWF .20 HP RRRRNQDRPSLLKKFREASWRFTFYLIAFIAGMAVIVDKPWFYDMKKVWEGYPIQSTIPS HR RKKNLVGRPTTLTKFQETFWRFAFYLTSFFYGLYVMYDQECVWQTEKCFSNYPEDHVLSQ detoke grant i rektor var i troch de destat

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	HP Q-YWYYMIELSFYWSLLFSIASDVKRKDFKEQIIHHVATIILISFSWFANYIRAGTLIMA
	* ** *** ** ** ** *** * * *** * * *** *
	HR KIYYYYLIELAFYSATTLTQFFDVKRKDFWEMFIHHIVTIILLCGSYTLNYTKMGAFILV
5	HP LHDSSDYLLESAKMFNYAGWKNTCNNIFIVFAIVFIITRLVILPFWILHCTLVYPLELYP
	.***.*. * *** .** * ** * ******.**.
	HR VHDSADFYIEFAKMGKYANNSLVTNVGFISFTISFFLSRLVILPLWIVPSIWFYGIYTYN
	HP AFFGYYFFNSMMGVLQLLHIFWAYLILRMAHKFITGKLVEDERSDREETESSEGEEAAAG
10	******* * * ****.
	HR CAMA-WLFCALL-ILQLLHFYWFSHIVKAAYASILVGVIERDTRSESEDSSAEDETAKYS
	HP GGAKSRPLANGHPILNNNHRKND
	*.
15	HR VGSGDYTESNGIHKRVVTAR

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T27334) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03499> (SEQ ID NOS: 5, 15 and 25)

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Determination of the whole base sequence of the cDNA insert of clone HP03499 obtained from cDNA library of human kidney revealed the structure consisting of a 129-bp 5'-untranslated region, a 1758-bp ORF, and a 86-bp 3'untranslated region. The ORF encodes a protein consisting of 585 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 63 kDa that was almost identical with the molecular weight of 63,987 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 82 kDa. In addition, there exist in the amino acid sequence of this protein five sites at which N-glycosylation may occur (Asn-Ile-Thr at position 89, Asn-Glu-Thr at position 106, Asn-Ala-Thr at position 189, Asn-Arg-Thr at position 220 and Asn-Ala-Thr at position 315).

The search of the protein database using the amino 20 acid sequence of the present protein revealed that the protein was similar to Chinese hamster hypothetical protein A30227). Table 7 shows 2BE2121 (Accession No. comparison between amino acid sequences of the human protein hamster of the present invention (HP) and Chinese 25 hypothetical protein 2BE2121 (CH). Therein, the marks of -,

	*, and . represent a gap, an amino acid residue ide	entical
•	with that of the protein of the present invention,	and an
	amino acid residue similar to that of the protein	of the
-	present invention, respectively. The both proteins sh	ared a
. 5	homology of 44.8% in the entire region.	•2
	Table 7	
	HP MVCREQLSKNQVKWVFAGITCVSVVVIAAIVLAITLRRPGCELEACSPDADMLDYLLSLG	
10	***. *	no mp. Novalles de
	CH SWSENILDYFLRNS	***
		.· •
	HP QISRRDALEVTWYHAANSKKAMTAALNSNITVLEADVNVEGLGTANETGVPIMAHPPTIY	
	**. *. ****** *. * . **. *	2 :
15	CH QITTEDGAEIIWYHAANHKSQMQEALRSAAHMIEADVLLPSDGSEHGQPIMAHPPEMN	٠
	HP SDNTLEQWLDAVLGSSQKGIKLDFKNIKAVGPSLDLLRQLTEEGKVRRPIWINADILKGP	
	*****. **. *. *. ********. * * *. *	
	CH SDNTLQEWLAEVM-KSNKGIKLDFKSLAAARASMLFLDNVKQHLQCPVWMNADVLPGP	
20		U L
	HP NMLISTEVNATQFLALVQEKYPKATLSPGWTTFYMSTSPNRTYTQAMVEKMHELVGGVPQ	
	* * * * * * * * * * * * * * * * * * * *	
	CH NG-SSKVVDAKAFLDTVTSFFPDVTFSLGWTTGWHPEKVNEGYSWTMVKEMDYICSGLTQ	
	restreet to the second of the	
25	HP RVTFPVRSSMVRAAWPHFSWLLSQSERYSLTLWQAASDPMSVEDLLYVRDNTAVHQVYYD	dī.

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HP IFEPLLSQFKQLALNATRKPMYYTGGSLIPLLQLPGDDGLNVEWLVPDVQGSGKTATMTL

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CH ILEPQSHEFKQAIGI

Furthermore, the search of the GenBank using the

base sequences of the present cDNA has revealed the
registration of sequences that shared a homology of 90% or
more (for example, Accession No. R92398) among ESTs. However,
since they are partial sequences, it can not be judged
whether or not they encode the same protein as the protein
of the present invention.

<HP03500> (SEQ ID NOS: 6, 16 and 26)

Determination of the whole base sequence of the cDNA insert of clone HP03500 obtained from cDNA library of human kidney revealed the structure consisting of a 134-bp 5'-untranslated region, a 996-bp ORF, and a 476-bp 3'-untranslated region. The ORF encodes a protein consisting of 331 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro

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translation resulted in formation of a translation product of 38 kDa that was almost identical with the molecular weight of 37,694 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the amino acid sequence of the protein matched with that of human hypothetical protein (Accession No. AAC05803) in which a region of 62 amino acid residues from glycine at position 88 to lysine at position 149 was deleted.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA340631) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10691> (SEQ ID NOS: 7, 17 and 27)

Determination of the whole base sequence of the cDNA insert of clone HP10691 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 246-bp 5'-untranslated region, a 1038-bp ORF, and a 1096-bp 3'-untranslated region. The ORF encodes a protein consisting of 345 amino acid residues and there existed at least two putative transmembrane domains. Figure, 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the

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Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human BB1 protein (Accession No. AAB37433). Table 8 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human BB1 protein (BB). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The C-terminal region of 215 amino acid residues of the present protein shared a homology of 81.9% with the N-terminal region of human BB1 protein.

Table 8

HP MSPEEWTYLVVLLISIPIGFLFKKAGPGLKRWGAAAVGLGLTLFTCGPHTLHSLVTILGT

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HP WALIQAQPCSCHALALAWTFSYLLFFRALSLLGLPTPTPFTNAVQLLLTLKLVSLASEVQ

HP DLHLAQRKEMASGFSKGPTLGLLPDVPSLMETLSYSYCYVGIMTGPFFRYRTYLDWLEQP

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125 BB 1411 MASGFSKGPTLGLLRRALPDGDT-QLQLLLRGNHDRPVLPLPHLPGLAGAA 45

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W48653) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10703> (SEQ ID NOS: 8, 18 and 28)

Determination of the whole base sequence of the cDNA insert of clone HP10703 obtained from cDNA library of human kidney revealed the structure consisting of a 359-bp

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5'-untranslated region, a 270-bp ORF, and a 1388-bp 3'untranslated region. The ORF encodes a protein consisting of 89 amino acid residues and there existed one putative transmembrane domain. Figure 8 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 18 kDa that was larger than the molecular weight of 10,469 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T08343) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10711> (SEQ ID NOS: 9, 19 and 29)

Determination of the whole base sequence of the cDNA insert of clone HP10711 obtained from cDNA library of human kidney revealed the structure consisting of a 29-bp 5'-untranslated region, a 1221-bp ORF, and a 356-bp 3'-untranslated region. The ORF encodes a protein consisting of 406 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the N-terminus. Figure 9 depicts the

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hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 44 kDa that was almost identical with the molecular weight of 43,836 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 58 kDa. In addition, there exist in the amino acid sequence of this protein seven sites at which N-glycosylation may occur (Asn-Ser-Thr at position 65, Asn-Trp-Ser at position 95, Asn-Val-Ser at position 134, Asn-Ile-Thr at position 159, Asn-Gly-Ser at position 187, Asn-Arg-Ser at position 230 and Asn-Leu-Thr at position 333). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glutamic acid at position 36.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to mouse kidney predominant protein (Accession No. BAA92527): Table 9 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse kidney predominant protein (MM). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the protein of the present invention, respectively. The

both proteins shared a homology of 79.9% in the entire region.

Table 9

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- 20 MM PTGAFANGSLTFKVQAFSRSGRPAQPPRLLHTADVCQLEVALVGASPRGNHSLFGLEVAT

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5 HS PPVDGLSPLVLGIMAVALGAPGLMLLGGGLVLLLHHKKYSEYQSIN

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MM PPVDIFSPLVLGIMAVALGAPGLMFLGGGLFLLLRHRRYSEYQSIN

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA362394) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10712> (SEQ ID NOS: 10, 20 and 30)

Determination of the whole base sequence of the cDNA insert of clone HP10712 obtained from cDNA library of human kidney revealed the structure consisting of a 52-bp 5'-untranslated region, a 579-bp ORF, and a 1064-bp 3'-untranslated region. The ORF encodes a protein consisting of 192 amino acid residues and there existed four putative transmembrane domains. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-

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Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to mouse calcium channel gamma 5 subunit (Accession No. CAB86387). Table 10 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse calcium channel gamma 5 subunit (MM). Therein, the marks of -, \*, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 75.0% in the entire region.

Table 10

25 MM WYFCTIGNHSEPHCLRDLSQAHMPGLAVGMGLARSVAAMAVVAAIFGLEMLIVSQVCEDV

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HS HSQCKWVMGSILLLVSFVLSSGGLLGFVILLRNQVTLIGFTLMFWCEFTASFLLFLNAIS

MM RSRRKWAIGSYLLLVAFILSSGGLLTFIILLKNQINLLGFTLMFWCEFTASFLFFLNAAS

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HS GLHINSITHPWE

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MM GLHINSLTQPWDPPAGTLAYRKRGYDGTSLI

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA910339) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<+ <+ <+ HP03010> (SEQ ID NOS: 31, 41 and 51)

Determination of the whole base sequence of the

CDNA insert of clone HPO3010 obtained from cDNA library of

human kidney revealed the structure consisting of a 97-bp

5'-untranslated region, a 1134-bp ORF, and a 320-bp 3'
untranslated region. The ORF encodes a protein consisting of

377 amino acid residues and there existed at least eight

putative transmembrane domains. Figure 11 depicts the

hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 42 kDa that was almost identical with the molecular weight of 41,462 predicted from the ORF as well as a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Arabidopsis thaliana hypothetical protein (Accession No. AAC34490). Table 11 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Arabidopsis thaliana hypothetical protein (AT). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 42.0% in the entire region other than the N-terminal region.

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Table 11

HP MDSALSDPHNGSAEAGGPTNSTTRPPSTPEGIALAYGSLLLMALLPIFFGALRSVRCARG

\* \* \*.

25 AT MKNCERFANLALAGLTLAPLVVRVNPNLNVILTACITVYVGCFRS

	HF	KNASDMPETITSRDAARFPIIASCTLLGLYLFFKIFSQEYINLLLSMYFFVLGILALSHT
		* *** * ***. * **. * . * .
	AT	VKDTPPTETMSKEHAMRFPLVGSAMLLSLFLLFKFLSKDLVNAVLTAYFFVLGIVALSAT
<sup></sup> 5		
	НР	ISPFMNKFFPASFPNRQYQLLFTQGSGENKEEIINYEFDTKDLVCLGLSSIVGVWYLLRK
		. * * *
	ΑT	LLPAIRRFLPNPWNDNLIVWRFPYFKSLEVEFTKSQVVAGIPGTFFCAWYAWKK
10	НР	HWIANNLFGLAFSLNGVELLHLNNVSTGCILLGGLFIYDVFWVFGTNVMVTVAKSFEAPI -
		**. ***. **. * *. * ** ***. ***. *** * ***. ****. ***
	ΑT	HWLANNILGLSFCIQGIEMLSLGSFKTGAILLAGLFFYDIFWVFFTPVMVSVAKSFDAPI
	НР	KLVFPQDLLEKGLEANNFAMLGLGDVVIPGIFIALLLRFDISLKKNTHTYFYTSFAAYIF
15		**. **
	AT	KLLFPTGDALRPYSMLGLGDIVIPGIFVALALRFDVSRRRQPQ-YFTSAFIGYAV
		en e
	ΗР	GLGLTIFIMHIFKHAQPALLYLVPACIGFPVLVALAKGEVTEMFSYEESNPKDPAAVTES
		*. *** * * ****** *** ***
20	ΑT	GVILTIVVMNWFQAAQPALLYIVPAVIGFLASHCIWNGDIKPLLAFDESKTEE-ATTDES
	HP	KEGTEASASKGLEKKEK
	•8	**
	AT	KTSEEVNKAHDE

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.... Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or (for example, Accession No. AA380429) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03576> (SEQ ID NOS: 32, 42 and 52)

Determination of the whole base sequence of the cDNA insert of clone HP03576 obtained from cDNA library of human kidney revealed the structure consisting of a 88-bp 5'-untranslated region, a 246-bp ORF, and a 1379-bp 3'untranslated region. The ORF encodes a protein consisting of 81 amino acid residues and there existed two putative 15 depicts the 12 domains. Figure transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kytethe present protein. In Doolittle method, of translation resulted in formation of a translation product of 20 kDa that was larger than the molecular weight of 9,178 20 predicted from the ORF.

. The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human vacuolar proton ATPase 9 kDa (Accession No. NP\_003936). Table 12 shows the comparison

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between amino acid sequences of the human protein of the present invention (HP) and human vacuolar proton ATPase 9 kDa (VP). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 71.2% in the entire region.

10 Table 12

HP MTAHSFALPVIIFTTFWGLVGIAGPWFVPKGPNRGVIITMLVATAVCCYLFWLIAILAQL

VP MAYHGLTVPLIVMSVFWGFVGFLVPWFIPKGPNRGVIITMLVTCSVCCYLFWLIAILAQL :

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HP NPLFGPQLKNETIWYVRFLWE

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VP NPLFGPQLKNETIWYLKYHWP

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W22566) among ESTs. However, since they are partial sequences, it can not be judged

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whether or not they encode the same protein as the protein of the present invention.

<HP03611> (SEQ ID NOS: 33, 43 and 53)

Determination of the whole base sequence of the cDNA insert of clone HP03611 obtained from cDNA library of human kidney revealed the structure consisting of a 189-bp 5'-untranslated region, a 1464-bp ORF, and a 105-bp 3'untranslated region. The ORF encodes a protein consisting of 487 amino acid residues and there existed eleven putative the 13 depicts Figure domains. transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human cystine/glutamate transporter (Accession No. BAA82628). Table 13 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human cystine/glutamate transporter (CG). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology

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of 43.8% in the entire region other than the N-terminal region.

Table 13

HP MGDTGLRKRREDEKSIQSQEPKTTSLQKELGLISGISIIVGTIIGS ..... \*.... \*.... \*. \*. \*. \*\*\* CG MVRKPVVSTISKGGYLQGNVNGRLPSLGNKEPPGQEKVQLKRKVTLLRGVSIIIGTIIGA 10 HP GIFVSPKSVLSNTEAVGPCLIIWAACGVLATLGALCFAELGTMITKSGGEYPYLMEAYGP \*\*\*, \*\*\*, \*\* \*\*, . \*\* . \*, . \*\*\*, . \*\*\*, . \*\*\*\* \*, \*\*\*\*, \*, \*, . \*, . \*\* CG GIFISPKGVLQNTGSVGMSLTIWTVCGVLSLFGALSYAELGTTIKKSGGHYTYILEVFGP HP IPAYLFSWASLIVIKPTSFAIICLSFSEYVCAPFYVGCKPPQIVVKCLAAAAILFISTVN 15 CG LPAFVRVWVELLIIRPAATAVISLAFGRYILEPFFIQCEIPELAIKLITAVGITVVMVLN HP SLSVRLGSYVQNIFTAAKLVIVAIIIISGLVLLAQGNTKNFDNSFEGAQLSVGAISLAFY 20 CG SMSVSWSARIQIFLTFCKLTAILIIIVPGVMQLIKGQTQNFKDAFSGRDSSITRLPLAFY Library and the control of the contr HP NGLWAYDGWNQLNYITEELRNPYRNLPLAIIIGIPLVTACYILMNVSYFTVMTATELLQS CG YGMYAYAGWFYLNFVTEEVENPEKTIPLAICISMAIVTIGYVLTNVAYFTTINAEELLLS

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CG MSEKITRTLQIILEVVPEEDKL

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R07056) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03612> (SEQ ID NOS: 34, 44 and 54)

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Determination of the whole base sequence of the cDNA insert of clone HP03612 obtained from cDNA library of human kidney revealed the structure consisting of a 153-bp 5'-untranslated region, a 1128-bp ORF, and a 269-bp 3'untranslated region. The ORF encodes a protein consisting of 375 amino acid residues and there existed seven putative transmembrane domains. Figure 14 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 39 kDa that was somewhat larger than the molecular weight of 37,930 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human monocarboxylate transporter (Accession No. AAC70919). Table 14 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human monocarboxylate transporter (MC). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 41.7% in the N-terminal region of 192 amino acid residues.

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# Table 14

	НР	MTPQPAGPPDGGWGWVVAAAAFAINGLSYGLLRSLGLAFPDLAEHFDRSAQDTAW
		.*. *******.*.*.* *.** * * *
5	МС	MPPMPSAPPVHPPPDGGWGWIVVGATFISIGFSYAFPKAVTVFFKEIQQIFHTTYSEIAW
	ΗР	ISALALAVQQAASPVGSALSTRWGARPVVMVGGVLASLGFVFSAFASGLLHLYLGLGLLA
		**. *** *. **. *. * * ****. * * * * *
	MC	ISSIMLAVMYAGGPVSSVLVNKYGSRPVVIAGGLLCCLGMVLASFSSSVVQLYLTMGFIT
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	HP	GFGWALVFAPALGTLSRYFSRRRVLAVGLALTGNGASSLLLAPALQLLLDTFGWRGALLL
		*. * * *** ** * ** * * **. *
	МС	GLGLAFNLQPALTIIGKYFYRKRPMANGLAMAGNPVFLSSLAPFNQYLFNTFGWKGSFLI
15	НР	LGAITLHLTPCGALLLPLVLPGDPPAPPRSPLAALGLSLFTRRAFSIFALGTALVGGGYF
		**, *, *, **
	MC	· LGSLLLNACVAGSLMRPLGPNQTTSKSKNKTGKTEDDSSPKKIKTKKSTWEKVNKYLDFS
	НР	VPYVHLAPRFRPGPGGIRSSAGGGRGCDGGCGRPAGLRVAGRPRLGAPPAAAGRIRGSDW
20		
	МС	LFKHRGFLIYLSGNVIMFLGFFAPIIFPAPYAKDQGIDEYSAAFLLSVMAFVDMFARPSV
		AGAVGGGAGARGGRRRELGGSPAGRGCGLWAERGELRPAGFRCTPRAGGRRRCGAGHRAG
	3.57	
2.5	. MC	GLIANSKYTRPRIOVEESEATMENGVCHLLCPLAODYTSLVLYAVEEGLGEGSVSSVLEE

### HP DDADEPRGAPGPSPVRLPKG

## MC TLMDLVGAPRFSSAVGLVTIVECGPVLLGPPLAGKLVDLTGEYKYMYMSCGAIVVAASVW

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI742291) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10407> (SEQ ID NOS: 35, 45 and 55)

Determination of the whole base sequence of the cDNA insert of clone HP10407 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 100-bp 5'-untranslated region, a 1053-bp ORF, and a 332-bp 3'-untranslated region. The ORF encodes a protein consisting of 350 amino acid residues and there existed at least four putative transmembrane domains. Figure 15 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein database using the amino acid sequence of the present protein revealed that the

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protein was longer by 35 amino acid residues at the N-terminus than human hypothetical protein (Accession No. CAB43375).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of a clone beginning from the 117th base of the present cDNA (Accession No. AL050274).

<HP10713> (SEQ ID NOS: 36, 46 and 56)

Determination of the whole base sequence of the cDNA insert of clone HP10713 obtained from cDNA library of human kidney revealed the structure consisting of a 79-bp 5'-untranslated region, a 2004-bp ORF, and a 611-bp 3'untranslated region. The ORF encodes a protein consisting of 667 amino acid residues and there existed nine putative domains. transmembrane Figure 16 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of present protein. the In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to mouse retinoic acid-responsive protein (Accession No. AAC16016). Table 15 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse retinoic acid-

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responsive protein (MM). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 74.1% in the entire region.

Table 15

HP MSSQPAGNQTSPGATEDYSYGSWYIDEPQGGEELQPEGEVPSCHTSIPPGLYHACLAS

\*, \*\*\*, \*, \*, \*\*\* \*\*\*\*, \*\* \*, \*\*\*, \* \*, . \*\*, \* \*\*\*\*\*

MM MESQASENGSQTSSGVTDDYS--SWYIEEPLGAEEVQPEGVIPLCQLTAPPALLHACLAS

HP LSILVLLLLAMLVRRRQLWPDCVRGRPGLPSPVDFLAGDRPRAVPAAVFMVLLSSLCLLL

\*\*, \*\*\*\*\*\*, \*\*\*\*, \*\*\* \* . . . \*\*\*\*\*\*\* . . . \*\*\*\*\* \* . . . \*\*\*\*\*

MM LSFLVLLLLALLVRRRRLWPRCGHRGLGLPSPVDFLAGDLSWTVPAAVFVVLFSNLCLLL

MM PDENPLPFLNLTAASSPDGEMETSRGPWKLLALLYYPALYYPLAACASAGHQAAFLLGTV

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MM LSWAHFGVQVWQKAECPQDPKIYKHYSLLASLPLLLGLGFLSLWYPVQLVQSLRHRTGAG

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		HP SKGLQSSYSEEYLRNLLCRKKLGSSYH-TSKHGFLSWARVCLRHCIYTPQPGFHLPLKLV
		*. ***. ****. ***. ***. * . ** **
		MM SQGLQTSYSEKYLRTLLCPKKLDSCSHPASKRSLLSRAWAFSHHSIYTPQPGFRLPLKLV
	5	HP LSATLTGTAIYQVALLLLVGVVPTIQKVRAGVTTDVSYLLAGFGIVLSEDKQEVVELVKH
		. *******. *******. ****. ***** ******
		MM ISATLTGTATYQVALLLLVSVVPTVQKVRAGINTDVSYLLAGFGIVLSEDRQEVVELVKH
		HP HLWALEVCYISALVLSCLLTFLVLMRSLVTHRTNLRALHRGAALDLSPLHRSPHPSRQAI
	10	***. *. ******** ***. *. ***. **. **. *
		MM HLWTVEACYISALVLSCASTFLLLIRSLRTHRANLQALHRGAALDLDPPLQSIHPSRQAI
•		
		HP FCWMSFSAYQTAFICLGLLVQQIIFFLGTTALAFLVLMPVLHGRNLLLFRSLESSWPFWL
		, ****, ***** *******, ******, *****, . *, *******, *****, ****
	15	MM VSWMSFCAYQTAFSCLGLLVQQVIFFLGTTSLAFLVFVPLLHGRNLLLLRSLESTWPFWL
		HP TLALAVILQNMAAHWVFLETHDGHPQLTNRRVLYAATFLLFPLNVLVGAMVATWRVLLSA
		*. ******* **. **. ** **. *. *. *****. *.
		MM TVALAVILQNIAANWIFLRTHHGYPELTNRRMLCVATFLLFPINMLVGAIMAVWRVLISS
	20	
		HP LYNAIHLGQMDLSLLPPRAATLDPGYYTYRNFLKIEVSQSHPAMTAFCSLLLQAQSLLPR
		***. ********* ***. ****. **. **. **. *
		MM LYNTVHLGQMDLSLLPQRAASLDPGYHTYQNFLRIEASQSHPGVIAFCALLLHAPSPQPR
. •	25	HP TMAAPQDSLRPGEEDEGMQLLQTKDSMAKGARPGASRGRARWGLAYTLLHNPTLQVFRKT

MM PPLAPQDSLRPAEEEEGMQLLQTKDLMAKGAGHKGSQSRARWGLAYTLLHNPSLQAFRKA

HP ALLGANGAQP

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MM ALTSAKANGTQP

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI760170) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10714> (SEQ ID NOS: 37, 47 and 57)

Determination of the whole base sequence of the cDNA insert of clone HP10714 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 82-bp 5'-untranslated region, a 1395-bp ORF, and a 1820-bp 3'-untranslated region. The ORF encodes a protein consisting of 464 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 17 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In

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vitro translation resulted in formation of a translation product of 49 kDa that was somewhat smaller than the molecular weight of 52,340 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 52 kDa. In addition, there exist in the amino acid sequence of this protein two sites at which N-glycosylation may occur (Asn-Ala-Thr at position 164 and Asn-Asp-Ser at position 320). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from threonine at position 22.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA861134) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10716> (SEQ ID NOS: 38, 48 and 58)

Determination of the whole base sequence of the cDNA insert of clone HP10716 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 60-bp 5'-untranslated region, a 1413-bp ORF, and a 653-bp 3'-untranslated region. The ORF encodes a protein consisting of 470 amino acid residues and there existed one

putative transmembrane domain at the N-terminus. Figure 18 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 61 kDa that was larger than the molecular weight of 52,086 predicted from the ORF.

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The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human hypothetical protein CGI-90 (Accession No. AAD34085). Table 16 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human hypothetical protein CGI-90 (CG). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 32.4% in the entire region.

20 Table 16

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HP-MSRLGALGGARAGLGLLLGTAAGLGFLCLLYSQRWKRTQRHGRSQSLPNSLDYTQTSDPG

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HP RHVMLLRAVPGGAGDASVLPSLPREGQEKVLDRLDFVLTSLVALRREVEELRSSLRGLAG

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	HP EIVGEVRCHMEENQRVARRRRFPFVRERSDSTGSSSVYFTASSGATFTDAESEGGYTTAN
	CG MALAARLWRLLPFRRGAAPGSRLPA
5	HP AESDNERDSDKESEDGEDEVSCETVKMGRKDSLDLEEEAASGASSALEAGGSSGLEDVLP
	.* *
	CG GPSGSRGIAAPARFRGFEVMGNPGTFNRGLLLSALSYLGFETYQVISQAAVVHATAKVEE
	HP LLQQADELHRGDEQGKREGFQLLLNNKLVYGSRQDFLWRLARAYSDMCELT-EEVSEKKS
10	.*.*** * * . *** . * ******
	CG ILEQADYLYESGETEKLYQLLTQYKESEDAELLWRLARASRDVAQLSRTSEEEKKL
· ·	HP YALDGKEEAEAALEKGDESADCHLWYAVLCGQLAEHESIQRRIQSGFSFKEHVDKAIALQ
	* * * **** * * ***
15	CG LVYEALEYAKRALEKNESSFASHKWYAICLSDVGDYEGIKAKIANAYIIKEHFEKAIELN
	HP PENPMAHFLLGRWCYQVSHLSWLEKKTATALLESPLSATVEDALQSFLKAEELQPGFSKA
	* * * ***** ** ** ** ** **.
	CG PKDATSIHLMGIWCYTFAEMPWYQRRIAKMLFATPPSSTYEKALGYFHRAEQVDPNFYSK
20	e, e e e e e e e e e e e e e e e e e e
	HP GRVYISKCYRELGKNSEARWWMKLALELPDVTKEDLAIQKDLEELEVILRD
	· · · · · · · · · · · · · · · · · · ·
	CG NLLLLGKTYLKLHNKKLAAFWLMKAKDYPAHTEEDKQIQTEAAQLLTSFSEKN

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA852295) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10717> (SEQ ID NOS: 39, 49 and 59)

Determination of the whole base sequence of the cDNA insert of clone HP10717 obtained from cDNA library of human kidney revealed the structure consisting of a 73-bp 5'-untranslated region, a 732-bp ORF, and a 976-bp 3'-untranslated region. The ORF encodes a protein consisting of 243 amino acid residues and there existed two putative transmembrane domains. Figure 19 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 36 kDa that was larger than the molecular weight of 26,270 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI478174) among ESTs. However, since they are partial sequences, it can not be judged whether or not they

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encode the same protein as the protein of the present invention.

<HP10718> (SEQ ID NOS: 40, 50 and 60)

Determination of the whole base sequence of the cDNA insert of clone HP10718 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 86-bp 5'-untranslated region, a 813-bp ORF, and a 889-bp 3'-untranslated region. The ORF encodes a protein consisting of 270 amino acid residues and there existed three putative transmembrane domains. Figure 20 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 28 kDa that was smaller than the molecular weight of 31,116 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Caenorhabditis elegans hypothetical protein Y53C10A (Accession No. CAA22139). Table 17 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Caenorhabditis elegans hypothetical protein Y53C10A (CE). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the

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present invention,	respectively. The both proteins shared a
homology of 54.8%	in the entire region other than the N-
terminal region.	•
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	•
НР	MAGAEDWPGQ
CE MTSSSAASSSTTTSSTMM	PDENECLKKEEERFKSPDPAPTLDEEVDIDTLPSMLEDDPNG
	.2.
HP QLELDEDEASCCRWGAQH	AGARELAALYSPGKRLQEWCSVILCFSLIAHNLVHLLLLARW :
***, **	***. **. ** . ***** * * ***. *
CE NVVECDLGFKGPRWGPQH	AGAKKLASMYSKEKRLQEKVSLFAAIFLFSIVFIN-LLLS-W

CE ESSIWVSVLVSAVLGIMTADFASGLVHWAADTFGSVE-TWFGRSFIRPFREHHVDPTAIT

HP RHDFIETNGDNCLVTLLPLLNMAYKFRTHSPEALEQ--LYPWECFVFCLIIFGTFTNQIH

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CE RHDIVEVNGDNCMLCVGPLLWILYQQMTYQRDAITQWATFHW--YILLLGIYVALTNQIH

25 CE KWSHTYFGLPTWVVFLQKAHIILPRSHHKIHHISPHACYYCITTGWLNWPLEYIGFWRKM

## HP EDLIQGLTGEKPRADDMKWAQKIK

\* .. . \*\* . \*\* . \*\* . \*\*

#### CE EWVVTTVTGMQPREDDLKWATKLQ

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or 10 (for example, Accession No. AA176107) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention. In addition, the region from position 466 to position 778 of the cDNA of the present 15 invention matched with the region from position 2 of human ubiquitin-conjugating enzyme position 314 variant 1 (Accession NO. NM\_003349) although no match was observed in another region.

<HP03745> (SEQ ID NOS: 61, 71 and 81)

Determination of the whole base sequence of the cDNA insert of clone HP03745 obtained from cDNA library of human kidney revealed the structure consisting of a 99-bp 5'-untranslated region, a 1170-bp ORF, and a 107-bp 3'-untranslated region. The ORF encodes a protein consisting of

25 389 amino acid residues and there existed at least nine

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putative transmembrane domains. Figure 21 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human solute carrier family 7 (Accession No. NP\_003974). Table 18 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human solute carrier family 7 (SC). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 36.0% in the N-terminal region of 397 amino acid residues.

Table 18

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MDRGEKIQLKRVFGYWWGTSFLLINIIG

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SC MEAREPGRPTPTYHLVPNTSQSQVEEDVSSPPQRSSETMQLKKEISLLNGVSLVVGNMIG

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25 HP-AGIFVSPKGVLAYSCMNVGVSLCVWAGCAILAMTSTLCSAEISISFPCSGAQYYFLKRYF

		. ********* *. ** ***
	SC	SGIFVSPKGVLVHT-ASYGMSLIVWAIGGLFSVVGALCYAELGTTITKSGASYAYILEAF
	НР	GSTVAFLNLWTSLFLGSGVVAG-QALLLAEYSIQPFFPSCSVPKLPKKCLALAMLWIVGI
5		* ** **
	SC	GGFIAFIRLWVSLLVVEPTGQAIIAITFANYIIQPSFPSCDPPYLACRLLAAACICLLTF
	HP	LTSRGVKEVTWLQIASSVLKVSILSFISLTGVVFLIRGKKENVERFQNAFDAELPDISHL
		** ** ** * * . *.* . *.**.* . **
10	SC	VNCAYVKWGTRVQDTFTYAKVVALIAIIVMGLVKLCQGHSEHFQDAFEGSSWDMGNL
	НР	IQAIFQGYFAYSGELKKPRTTIPKCIFTALPLVTVVYLLVNISYLTVLTPR
	t	* *. ***
	SC	SLALYSALFSYSGWDTLNFVTEEIKNPERNLPLAIGISMPIVTLIYILTNVAYYTVLNIS
15		
	• нр	EILSSDAVAITWADRAFPSLAWIMPFAISTSLFSNLLISIFKSSRPIYLASQEGQLPLLF
		****** *
	SC	DVLSSDAVAVTFADQTFGMFSWTIPIAVALSCFGGLNASIFASSRLFFVGSREGHLPDLL
20	HP	NTLNSHS-SPFTAVLLLVTLGSLAIILTSLIDLINYIFFTGSLWSILLMIGILRRRYQEP
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	SC	SMIHIERFTPIPALLFNCTMALIYLIVEDVFQLINYFSFSYWFFVGLSVVGQLYLRWKEP
	HP	NLSIPYKVKLDF

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# SC KRPRPLKLSVFFPIVFCICSVFLVIVPLFTDTINSLIGIGIALSGVPFYFMGVYLPESRR

<HP03747> (SEQ ID NOS: 62, 72 and 82)

Determination of the whole base sequence of the cDNA insert of clone HP03747 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 21-bp 5'-untranslated region, a 1047-bp ORF, and a 1324-bp 3'-untranslated region. The ORF encodes a protein consisting of 348 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 22 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 40 kDa that was almost identical with the molecular weight of 39,685 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from proline at position 39.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human endoplasmic reticulum glycoprotein (Accession No. NP\_006807). Table 19 shows the comparison between amino acid sequences of the human protein

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of the present invention (HP) and human endoplasmic reticulum glycoprotein (ER). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 54.1% in the entire region.

Table 19

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HP MAATLGPLGSWQ-QW-RRCLSARD-----GSRMLLLLLLLGSGQGPQQVGAGQTFEYLK

\*. \* \*\*\*\* \* . . . \*. \*. \*\*\*\*

ER MAAEGWIWRWGWGRRCLGRPGLLGPGPGPTTPLFLLLL-LGSVTADITDGNS-EHLK

ER REHSLIKPYQGVGSSSMPLWDFQGSTMLTSQYVRLTPDERSKEGSIWNHQPCFLKDWEMH

- HP VHFKIHGQGKKNLHGDGLAIWYTKDRMQPGPVFGNMDKFVGLGVFVDTYPNEEKQQERVF

  \*\*\*\*. \*\* \*\*\*\*\*\*\*\*\*. \*. \*\*\*\*\*\*. \*. \* \*\*. \* \*\*\*\*\*

  ER VHFKVHGTGKKNLHGDGIALWYTRDRLVPGPVFGSKDNFHGLAIFLDTYPNDET-TERVF
- ER PYISVMVNNGSLSYDHSKDGRWTELAGCTADFRNRDHDTFLAVRYSRGRLTVMTDLEDKN

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA262924) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10719> (SEQ ID NOS: 63, 73 and 83)

Determination of the whole base sequence of the cDNA insert of clone HP10719 obtained from cDNA library of human kidney revealed the structure consisting of a 54-bp

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5'-untranslated region, a 786-bp ORF, and a 576-bp 3'-untranslated region. The ORF encodes a protein consisting of 261 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 23 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 33 kDa that was larger than the molecular weight of 27,435 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from asparagine at position 19.

acid sequence of the present protein revealed that the protein was similar to mouse endomucin (Accession No. AAD05208). Table 20 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse endomucin (MM). Therein, the marks of -, \*, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 47.9% in the entire region.

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	MELLQVTIL-FLLP-SIC-SSNSTGVL-EAANNSLVVTTTKPSITTPNTESLQKNVVTPT
	* *** * * *** * * * *
M	MRLLQATVLFFLLSNSLCHSEDGKDVQNDSIPTPAETSTTKASVTIPGIVSV-TNPNKPA
Н	P TGTTPKGTITNELLKMSLMSTATFLTSKDEGLKATTTDVRKNDSIISNVTVTSVTLPNAV
	. **. *. ** **
M	M DGTPPEGTTKSDVSQTSLVTTINSLTTPKHEVGTTTEGPLRNESSTMKITVPNTPTSNAN
Н	P STLQSSKPKTETQSSIKTTEIPGSVLQPDASPSKTGTLTSIPVTIPENTSQSQVIGTEGG
	***. *. *. **. **. **. **. **.
M	M STLPGSQNKITTQLLDALPKITATPSASLTTAHTMSLLQDTEDR
H	P KNASTSATSRSYSSIILPVVIALIVITLSVFVLVGLYRMCWKADPGTPENGNDQPQSDKE
	* * * * * * * * * * * * * * * * * * * *
M	M KIATTPSTTPSYSSIILPVVIALVVITLLVFTLVGLYRICWKRDPGTPENGNDQPQSDKE
ŀ	IP SVKLLTVKTISHESGEHSAQGKTKN
	************
ì	M SVKLLTVKTISHESGEHSAQGKTKN

sequences that shared a homology of 90% or more (for example, Accession No. AA486620) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10720> (SEQ ID NOS: 64, 74 and 84)

Determination of the whole base sequence of the cDNA insert of clone HP10720 obtained from cDNA library of human kidney revealed the structure consisting of a 25-bp 10 5'-untranslated region, a 669-bp ORF, and a 653-bp 3'untranslated region. The ORF encodes a protein consisting of amino acid residues and there existed a putative secretory signal at the N-terminus and one transmembrane domain in the inner portion. Figure 24 depicts 15. the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 28 kDa that was somewhat larger than the molecular weight of 25,219 predicted from the ORF. In this case, the addition 20 of a microsome led to the formation of a product of 35 kDa. In addition, there exist in the amino acid sequence of this protein two sites at which N-glycosylation may occur (Asn-Val-Thr at position 76 and Asn-His-Thr at position 93). Application of the (-3,-1) rule, a method for predicting the 25 cleavage site of the secretory signal sequence, allows to

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expect that the mature protein starts from glutamic acid at position 15.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI792241) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

10 <HP10721> (SEQ ID NOS: 65, 75 and 85)

Determination of the whole base sequence of, the CDNA insert of clone HP10721 obtained from cDNA library of human kidney revealed the structure consisting of a 74-bp 5'-untranslated region, a 552-bp ORF, and a 1658-bp 3'-untranslated region. The ORF encodes a protein consisting of 183 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 25 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 23 kDa that was somewhat larger than the molecular weight of 19,989 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 22 kDa. Application of the (-3,-1) rule, a method for predicting the

25 Application of the (-3,-1) rule, a method for predicting the

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cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glutamic acid at position 25.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R27187) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10725> (SEQ ID NOS: 66, 76 and 86)

Determination of the whole base sequence of the cDNA insert of clone HP10725 obtained from cDNA library of human kidney revealed the structure consisting of a 235-bp 5'-untranslated region, a 789-bp ORF, and a 713-bp 3'-untranslated region. The ORF encodes a protein consisting of 262 amino acid residues and there existed one putative transmembrane domain. Figure 26 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example,

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Accession No. AI127782) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10727> (SEQ ID NOS: 67, 77 and 87)

Determination of the whole base sequence of the cDNA insert of clone HP10727 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 102-bp 5'-untranslated region, a 507-bp ORF, and a 947bp 3'-untranslated region. The ORF encodes a protein consisting of 168 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 27 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 24 kDa that was larger than the molecular weight of 17,822 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 23 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from lysine at position 29.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of

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sequences that shared a homology of 90% or more (for example, Accession No. R80316) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10728> (SEQ ID NOS: 68, 78 and 88)

Determination of the whole base sequence of the cDNA insert of clone HP10728 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 221-bp 5'-untranslated region, a 732-bp ORF, and a 902-bp 3'-untranslated region. The ORF encodes a protein consisting of 243 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 28 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 30 kDa that was larger than the molecular weight of 26,534 predicted from the ORF.

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H23535) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10730> (SEQ ID NOS: 69, 79 and 89)

Determination of the whole base sequence of the cDNA insert of clone HP10730 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 27-bp 5'-untranslated region, a 1287-bp ORF, and a 1216-bp 3'-untranslated region. The ORF encodes a protein consisting of 428 amino acid residues and there existed one putative transmembrane domain. Figure 29 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 50 kDa that was somewhat larger than the molecular weight of 48,992 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. C19105) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10742> (SEQ ID NOS: 70, 80 and 90)

Determination of the whole base sequence of the cDNA insert of clone HP10742 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 231-bp 5'-untranslated region, a 852-bp ORF, and a 828-

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bp 3'-untranslated region. The ORF encodes a protein consisting of 283 amino acid residues and there existed two putative transmembrane domains. Figure 30 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 30 kDa that was smaller than the molecular weight of 31,629 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T35949) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

## <HP03800> (SEQ ID NOS: 91, 101 and 111)

Determination of the whole base sequence of the cDNA insert of clone HP03800 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 67-bp 5'-untranslated region, a 1431-bp ORF, and a 135-bp 3'-untranslated region. The ORF encodes a protein consisting of 476 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 31 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In

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vitro translation resulted in formation of a translation product of 55 kDa that was almost identical with the molecular weight of 54,110 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 58 kDa. In addition, there exist in the amino acid sequence of this protein four sites at which N-glycosylation may occur (Asn-Lys-Thr at position 81, Asn-Met-Thr at position 132, Asn-Val-Thr at position 307 and Asn-Gln-Thr at position 346). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from leucine at position 23.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to mosquito vitellogenic carboxypeptidase (Accession No. P42660). Table 21 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mosquito vitellogenic carboxypeptidase (VC). Therein, the marks of -, \*, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 44.5% in the entire region. In addition, the C-terminal portion beginning from alanine at position 182 matched with

human probable carboxypeptidase (Accession No. AAC23787) except one amino acid residue. Table 21 5 HP MVGAMWKVIVSLVLLMPGPCDGLFRSLYRSVSMPPK-GDSGQPLFLTPYIEAGKIQKG ...\* \*. . \*\*. \*.\*\*\*\*\*\* ... \*\*\*... VC MVKFHLLVLIAFTCYTCSDATLWNPYKKLMRGSASPPRPGESGEPLFLTPLLQDGKIEEA 10 HP RELSLYGPFPGLNMKSYAGFLTVNKTYNSNLFFWFFPAQIQPEDAPVVLWLQGGPGGSSM VC RNKARVNHPMLSSVESYSGFMTVDAKHNSNLFFWYVPAKNNREQAPILVWLQGGPGASSL HP FGLFVEHGPYVVTSNMTLRDRDFPWTTTLSMLYIDNPVGTGFSFTDDTHGYAVNEDDVAR 15 VC FGMFEENGPFH1HRNKSVKQREYSWHQNHHM1Y1DNPVGTGFSFTDSDEGYSTNEEHVGE HP DLYSALIQFFQIFPEYKNNDFYVTGESYAGKYVPAIAHLIHSLNPVREVKINLNGIAIGD . \* . . \*\*\* . \*\* . . \*\*, . \*\*\*, \*\*, \*\*\*, . . \*\* \* . . . \*\*\*\*, \* . . . \*\*\*\* 20 VC NLMKFIQQFFVLFPNLLKHPFYISGESYGGKFVPAFGYAIH--NSQSQPKINLQGLAIGD \* HP GYSDPESIIGGYAEFLYQIGLLDEKQKKYFQKQCHECIEHIRKQNWFEAFEILDKLLDGD 

VC GYTDPLNQL-NYGEYLYELGLIDLNGRKKFDEDTAAAIACAERKDMNSANRLIQGLFDG-

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НР	LTSDPSYFQNVTGCSNYYNFLRC-TEPEDQLYYVKFLSLPEVRQAIHVGNQTFNDGTIVE
	* ***. *** *. **** * *** **** *.*
VC	LDGQESYFKKVTGFSSYYNFIKGDEESKQDSVLMEFLSNPEVRKGIHVGELPFHDSDGHN
НР	KYLREDTVQSVKPWLTEIMNNYKVLIYNGQLDIIVAAALTEHSLMGMDWKGSQEYKK
	* * *** * * **
VC	KVAEMLSEDTLDTVAPWVSKLLSHYRVLFYNGQLDIICAYPMTVDFLMKMPFDGDSEYKR
HP	AEKKVWKIFKSDSEVAGYIRQAGDFHQVIIRGGGHILPYDQPLRAFDMINRFIYGKGWDF
	* * . * . * * * * * * * * * * * * *
<b>V</b> C	ANREIYRVDGEIAGYKKRAGRLQEVLIRNAGHMVPRDQPKWAFDMITSFTHKNYL
HP	YVG

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA095665) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present Company of the second second invention.

<HP03831> (SEQ ID NOS: 92, 102 and 112)

Determination of the whole base sequence of the cDNA insert of clone HP03831 obtained from cDNA library of 25

human kidney revealed the structure consisting of a 191-bp 5'-untranslated region, a 681-bp ORF, and a 223-bp 3'-untranslated region. The ORF encodes a protein consisting of 226 amino acid residues and there existed four putative transmembrane domains. Figure 32 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

10 The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human claudin-10 (Accession No. NP\_008915). Table 22 shows the comparison between amino acid sequences of the human protein of the present invention 15 (HP) and human claudin-10 (CD). Therein, the marks of -,  $\star$ , and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology 20 of 76.2% in the entire region. The C-terminal region downstream from glycine at position 72 completely matched with that sequence.

Table 22

	HP MSRAQIWALVSGVGGFGALVAATTSNEWKVTTRASSVITATWVYQGLWMNCAGNALGS	
	. * * * ***. * ***. * *	
	CD MASTASEIIAFMVSISGWVLVSSTLPTDYWKVSTIDGTVITTATYWANLWKACVTDSTGV	·
5	HP FHCRPHFTIFKVAGYIQACRGLMIAAVSLGFFGSIFALFGMKCTKVGGSDKAKAKIACLA	
	· * · · · · · · · · · · · · · · · · · ·	
	CD SNCKDFPSMLALDGYIQACRGLMIAAVSLGFFGSIFALFGMKCTKVGGSDKAKAKIACLA	
	HP GIVFILSGLCSMTGCSLYANKITTEFFDPLFVEQKYELGAALFIGWAGASLCIIGGVIFC	
10	******************	4 ,
	CD GIVFILSGLCSMTGCSLYANKITTEFFDPLFVEQKYELGAALFIGWAGASLCIIGGVIFC	7,*
	HP FSISDNNKTPRYTYNGATSVMSSRTKYHGGEDFKTTNPSKQFDKNAYV	
	******************	1
15	CD FSISDNNKTPRYTYNGATSVMSSRTKYHGGEDFKTTNPSKQFDKNAYV	:

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N41613) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

25... <HP03879> (SEQ ID NOS: 93, 103 and 113) \_\_ ===

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Determination of the whole base sequence of the cDNA insert of clone HP03879 obtained from cDNA library of human kidney revealed the structure consisting of a 33-bp 5'-untranslated region, a 918-bp ORF, and a 651-bp 3'-untranslated region. The ORF encodes a protein consisting of 305 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 33 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 34 kDa that was almost identical with the molecular weight of 34,073 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human NADH-cytochrome b5 reductase (Accession No. Y09501). Table 23 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human NADH-cytochrome reductase (CT). Therein, the marks of -,  $\star$ , and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 63.5% in the entire region other than the N-terminal region.

٠, .

Table 23

	HP MGIQTSPVLLASLGVGLVTLLGLAVGSYLVRRSRRPQVTLLDPNEKYLLRLLDKTTVSHN
	* ** * * * ** ** ** ** ***. **. **.
5	CT MGAQLSTLGHMVLFPVWFLYSLLMKLFQRS-TPAITLESPDIKYPLRLIDREIISHD
	HP TKRFRFALPTAHHTLGLPVGKHIYLSTRIDGSLVIRPYTPVTSDEDQGYVDLVIKVYLKG
	* ****** * * * ***** * * * * * * * * * *
	CT TRRFRFALPSPQHILGLPVGQHIYLSARIDGNLVVRPYTPISSDDDKGFVDLVIKVYFKD
10	
	HP VHPKFPEGGKMSQYLDSLKVGDVVEFRGPSGLLTYTGKGHFNIQPNKKSPPEPRVAKKLG
	***** ****** * ** . ******* * *** * *
	CT THPKFPAGGKMSQYLESMQIGDTIEFRGPSGLLVYQGKGKFAIRPDKKSNPIIRTVKSVG
•	
15	HP MIAGGTGITPMLQLIRAILKVPEDPTQCFLLFANQTEKDIILREDLEELQARYPNRFKLW
	***********************************
	CT MIAGGTGITPMLQVIRAIMKDPDDHTVCHLLFANQTEKDILLRPELEELRNKHSARFKLW
	HP FTLDHPPKDWAYSKGFVTADMIREHLPAPGDDVLVLLCGPPPMVQLACHPNLDKLGYSQK
20	. ***. * . * . * . * . * *** . *** . * *** . * * * * ** *
	CT YTLDRAPEAWDYGQGFVNEEMIRDHLPPPEEEPLVLMCGPPPMIQYACLPNLDHVGHPTE
	HP MRFTY
	10 20 <b>*</b>
25	CT DCEVE

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. F06459) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

10 <HP03880> (SEQ ID NOS: 94, 104 and 114)

Determination of the whole base sequence of the cDNA insert of clone HP03880 obtained from cDNA library of human kidney revealed the structure consisting of a 98-bp 5'-untranslated region, a 684-bp ORF, and a 115-bp 3'untranslated region. The ORF encodes a protein consisting of 227 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 34 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 28 kDa that was somewhat larger than the molecular weight of 25,717 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 27 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to

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expect that the mature protein starts from aspartic acid at position 23.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to rat phosphatidylethanolamine-binding protein (Accession No. P31044). Table 24 shows the comparison between amino acid sequences of the human protein invention (HP) and rat of present the phosphatidylethanolamine-binding protein (RN). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.6% in the region of 133 amino acid residues other than the N-terminal region.

Table 24

HP MGWTMRLVTAALLLGLMMVVTGDEDENSPCAHEALLDEDTLFCQGLEVFYPELGNIGCKV

RN MAADISQWAGPLSLQEVDEPPQHALRVDYGGVTV

HP VPDCNNYRQKITSWMEPIVKFPGAVDGATYILVMVDPDAPSRAEPRQRFWRHWLVTDIKG

RN DELGKVLTPTQVMNRPSSISWDGLDPGKLYTLVLTDPDAPSRKDPKFREWHHFLVVNMKG

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HP ADLKKGKIOGOELSAYOAPSPPAHSGFHRYOFFVYLOEGKV---ISLLP-KENKTRGSWK

\*\*..\*. \*\*. \*\*.. \*\* ... \*\* ... \*\* ... \*\* ... \*\*...

RN NDISSGTV----LSEYVGSGPPKDTGLHRYVWLVYEQEQPLNCDEPILSNKSGDNRGKFK

5

HP MDRFLNRFHLGEPEASTQFMTQNYQDSPTLQAPRERASEPKHKNQAEIAAC

...\* ... \*\*\*. \* \*. \* . . . . \*. \*.

RN VESFRKKYHLGAPVAGTCFQAEWDDSVPKLHDQLAGK

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H83784) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10704> (SEQ ID NOS: 95, 105 and 115)

Determination of the whole base sequence of the

CDNA insert of clone HP10704 obtained from cDNA library of
human kidney revealed the structure consisting of a 141-bp
5'-untranslated region, a 1326-bp ORF, and a 399-bp 3'untranslated region. The ORF encodes a protein consisting of
441 amino acid residues and there existed eight putative
transmembrane domains. Figure 35 depicts the

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hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human unknown gene product (Accession No. AAC27544). Table 25 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human unknown gene product (UP). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.1% in the entire region.

Table 25

HP MAIHKALVMCLGLPLFLFPG-AWAQGHVPPGCSQGLNPLYYNLCDRSGAWGIVLE

20 \* \*\*... \* ... \*\* . \* \* \* \* \* \*\*\*\*.\*

UN MFVASERKMRAHQVLTFLLLFVITSVASENASTSRGCGLDLLPQYVSLCDLDAIWGIVVE

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25 UN-AVAGAGALITLLLMLILLVRLPFIKEKEKKSPVGLHFLFLLGTLGLFGLTFAFIIQEDET (# )

HP TCASRRFLFGVLFAICFSCLAAHVFALNFLARKNHGPRGWVIFTVALLLTLVEVIINTE
.*. ****. ***** *.*. *. ** ** ** * **. **
UN ICSVRRFLWGVLFALCFSCLLSQAWRVRRLVRHGTGPAGWQLVGLALCLMLVQVIIAVE
HP LIITLVRGSGEGGPQGNSSAGWAVASPCAIANMDFVMALIYVMLLLLGAFLGAWPALCG
*** * * * * * * * *
UN LVLTVLRDTRPACAYEPMDFVMALIYDMVLLVVTLGLALFTLCG
HP YKRWRKHGVFVLLTTATSVAIWVVWIVMYTYGN-KQHNSPTWDDPTLAIALAANAWAFV
. *** *. *. *. ** ***. * ** *
UN FKRWKLNGAFLLITAFLSVLIWVAWMTMYLFGNVKLQQGDAWNDPTLAITLAASGWVFV
HP FYVIPEVSQVTKSSPEQSYQGDMYPTRGVGY-ETILKEQ-KGQSMFVENKAFSMDEPVA
*, *** * *
UN FHAIPEI-HCTLLPALQENTPNYFDTSQPRMRETAFEEDVQLPRAYMENKAFSMDEHNA
HP KRPVS-PYSGYNGQLLTSVYQPTEMALMHKVPSEGAYDIILPRATANSQVMGSANSTLR
* *
UN LRTAGFPNGSLGKRPSGSLGKRPSAPFRSNVYQPTEMAVVLNGGTIPTAPPSHTGRHLW
AR Mark to the first of the second of the se
HP EDMYSAQSHQAATPPKDGKNSQVFRNPYVWD

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of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA346702) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10715> (SEQ ID NOS: 96, 106 and 116)

Determination of the whole base sequence of the cDNA insert of clone HP10715 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 49-bp 5'-untranslated region, a 798-bp ORF, and a 1351-bp 3'-untranslated region. The ORF encodes a protein consisting of 265 amino acid residues and there existed two putative transmembrane domains. Figure 36 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 43 kDa that was larger than the molecular weight of 29,217 predicted from the ORF.

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI381750) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present

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invention.

<HP10724> (SEQ ID NOS: 97, 107 and 117)

Determination of the whole base sequence of the cDNA insert of clone HP10724 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 68-bp 5'-untranslated region, a 627-bp ORF, and a 1485-bp 3'-untranslated region. The ORF encodes a protein consisting of 208 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 37 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 24 kDa that was almost identical with the molecular weight of 23,850 predicted from the ORF.

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T78035) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10733> (SEQ ID NOS: 98, 108 and 118)

Determination of the whole base sequence of the cDNA insert of clone HP10733 obtained from cDNA library of human umbilical cord blood revealed the structure consisting

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of a 102-bp 5'-untranslated region, a 1203-bp ORF, and a 222-bp 3'-untranslated region. The ORF encodes a protein consisting of 400 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 38 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 50 kDa that was larger than the molecular weight of 43,151 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 54 kDa. In addition, there exist in the amino acid sequence of this protein four sites at which N-glycosylation may occur (Asn-Leu-Thr at position 52, Asn-Ala-Ser at position 131, Asn-Ile-Thr at position 145 and Asn-Leu-Ser at position 343). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from arginine at position 33.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Drosophila melanogaster GOLIATH protein (Accession No. Q06003). Table 26 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Drosophila melanogaster

GOLIATH protein (DM). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.0% in the entire region.

Table 26

10	HP MAWRREASVGARGVLALALLALALCVPGARGRALEWFSAVVNIEYVDPQTNLTV	/WSVSE
	HP SGRFGDSSPKEGAHGLVGVPWAPGGDLEGCAPDTRFFVPEPGGRGAAPWVALVAF	RGGCTF
	IP KDKVLVAARRNASAVVLYNEERYGNITLPMSHAGTGNIVVIMISYPKGREILEL-	-VQKGI
. 5	* **.*.*	**
	MQLEKMQIKGKTRNIAAVITYQNIGQDLSLT	LDKGY
	IP PVTMTIGVGTRHVQEFISGQSVVFVAIAFITMMIISLAWLIFYYIQRFLY-TG	SQIGS
	*** * * * **.**. * * ******* * .	*
0	DM NVTISIIEGRRGVRTISSLNRTSVLFVSISFIVDDILCWLIFYYIQRFRYMQA	KDQQS
	e e <del>e e e</del> e e e e e e e e e e e e e e	
	P QSHRKETKKVIGQLLLHTVKHGEKGIDVDAENCAVCIENFKVKDIIRILPCKHIF	HRICI
	***, * * * * **. **	*. **
	M RNLCSVTKKAIMKIPTKTGKFSD-EKDLDSDCCAICIEAYKPTDTIRILPCKHEF	'HKNCI
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	НР	DPWLLDHRTCPMCKLDVIKALGYWGEPGDVQEMPAPESPPGRDPAANLSLALPDDDGSDE
	•	****
	DM	DPWLIEHRTCPMCKLDVLKFYGY-VVGDQIYQTPSPQHTAPIASIEEVPVIVVAVPHGPQ
	•	
5	HР	SSPPSASPAESEPQCDPSFKGDAGENTALLEAGRSDSRHGGPIS
		* * *
	DM	PLQPLQASNMSSFAPSHYFQSSRSPSSSVQQQLAPLTYQPHPQQAASERGRRNSAPATMP

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI286184) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10734> (SEQ ID NOS: 99, 109 and 119)

Determination of the whole base sequence of the cDNA insert of clone HP10734 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 124-bp 5'-untranslated region, a 579-bp ORF, and a 1202-bp 3'-untranslated region. The ORF encodes a protein consisting of 192 amino acid residues and there existed one putative transmembrane domain. Figure 39 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-

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Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human sodium channel ß2 subunit (Accession No. AAD47196). Table 27 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human sodium channel ß2 subunit (SC). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 26.3% in the N-terminal region of 152 amino acid residues.

Table 27

HP DOGTYICEIRLKGESQYFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVE

SC DEGIYNCYIMNPPDRHRGHGKIHLQVLMEEPPERDFTVAVIVGASVGGFLAVVILVLMVV

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HP WIFSGRRAKVTRRKHHCVREGSG

SC KCVRRKKEQKLSTDDLKTEEEGKTDGEGNPDDGAK

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. C03216) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10756> (SEQ ID NOS: 100, 110 and 120)

Determination of the whole base sequence of the

CDNA insert of clone HP10756 obtained from cDNA library of
human kidney revealed the structure consisting of a 49-bp
5'-untranslated region, a 783-bp ORF, and a 166-bp 3'untranslated region. The ORF encodes a protein consisting of
260 amino acid residues and there existed a putative
secretory signal at the N-terminus. Figure 40 depicts; the

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hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was almost identical with the molecular weight of 27,356 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AW027769) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03670> (SEQ ID NOS: 121, 131 and 141)

Determination of the whole base sequence of the cDNA insert of clone HP03670 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 77-bp 5'-untranslated region, a 1014-bp ORF, and a 531-bp 3'-untranslated region. The ORF encodes a protein consisting of 337 amino acid residues and there existed at least seven putative transmembrane domains. Figure 41 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human hypothetical protein KIAA0260

(Accession No. BAA13390). Table 28 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human hypothetical protein KIAA0260 (KI). Therein, the marks of -, \*, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 57.6% in the entire region other than the N-terminal region. In addition, the C-terminal region beginning from leucine at position 77 matched with human putative Sqv-7-like protein (Accession No. AJ005866) except one amino acid residue.

Table 28

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HP MTAGGQAEAEGAGGEPG

KI NSWSPLGAAAAGPRAARPRRQATAAAAAMAEVHRRQHARVKGEAPAKSSTLRDEEELGMA

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HP NKIIHFPDFDKKIPVKLFPLPLLYVGNHISGLSSTSKLSLPMFTVLRKFTIPLTLLLETI

- KI LRVVKFPDLDRNVPRKTFPLPLLYFGNQITGLFSTKKLNLPMFTVLRRFSILFTMFAEGV
- HP ILGKQYSLNIILSVFAIILGAFIAAGSDLAFNLEGYIFVFLNDIFTAANGVYTKQKMDPK
  .\* \* .\* . \* . \* \* . \* \* . \* \* . \* \* . \* \* . \* \* . \* . \* \* . \* . \* \* . \* . \* \* . \* . \* \* . \* . \* \* . \*
- 5 KI LLKKTFSWGIKMTVFAMIIGAFVAASSDLAFDLEGYAFILINDVLTAANGAYVKQKLDSK

  - KI ELGKYGLLYYNALFMILPTLAIAYFTGDAQKAVEFEGWADTLFLLQFTLSCVMGFILMYA
  - HP TVLCSYYNSALTTAVVGAIKNVSVAYIGILIGGDYIFSLLNFVGLNICMAGGLRYSFLTL

    \*\*\*\*. \*\*\*\*\*\*\*..\*\* \*\*\*...\*\*\*\*\*... \*\*...\*\*\*\*...\*\*

    KI TVLCTQYNSALTTTIVGCIKNILITYIGMVFGGDYIFTWTNFIGLNISIAGSLVYSYITF
- 15 HP SSQLKPKPVGEENICLDLKS
  - ... \* \* \* \*\* \*\*
  - KI TEEQLSKQ-SEANNKLDIKGKGAV

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R24922) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present

invention.

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<HP03688> (SEQ ID NOS: 122, 132 and 142)

Determination of the whole base sequence of the cDNA insert of clone HPO3688 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 35-bp 5'-untranslated region, a 711-bp ORF, and a 1729-bp 3'-untranslated region. The ORF encodes a protein consisting of 236 amino acid residues and there existed five putative transmembrane domains. Figure 42 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Caenorhabditis elegans hypothetical protein W02D9 (Accession No. CAB03470). Table 29 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Caenorhabditis elegans hypothetical protein W02D9 (CE). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 50.8% in the entire region other than the N-terminal

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		region
		Table 29
	5	HP MAEAEE
		CE MEILNLSSKFSLSDKPCQKFIFSLFSAVQNSRFKIISFPEIHQKPLPQEEMNSFGNASVD
	LO	HP SPGDPGTASPRPLFAGLSDISISQDIPVEGEITIPMRSRIREFDSSTLNESVRNTIMRDL
		CE IDMLEQEMAAEQTANLSGNIAGMSAPKSSSNRRGPMQEVDLDAEFDTLEEPVWDTVKRDV
	,	HP KAVGKKFMHVLYPR-KSNTLLRDWDLWGPLILCVTLALMLQRDSADSEKDGGPQFAEVFV
. 1	L 5	. ** ** **. * **********. **. **.
	-	HP IVWFGAVTITLNSKLLGGNISFFQSLCVLGYCILPLTVAMLICRLVLLADPGPVNFMVRL  ***.*.* * *************************
	20	CE ITFFGSVIVTANIKLLGGNISFFQSLCVIGYCLLPPFVAAVLCSL-FLHGIAFPLRL
		HP-FVVIVMFAWSIVASTAFLADSQPPNRRALAVYPVFLFYFVISWMILTFTPQ ,
	-	CE LITSIGFVWSTYASMGFLAGCQPDKKRLLVIYPVFLFYFVVSWMIISHS

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T51465) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03825> (SEQ ID NOS: 123, 133 and 143)

Determination of the whole base sequence of the cDNA insert of clone HP03825 obtained from cDNA library of human kidney revealed the structure consisting of a 20-bp 5'-untranslated region, a 1683-bp ORF, and a 36-bp 3'untranslated region. The ORF encodes a protein consisting of 560 amino acid residues and there existed seven putative 15 Figure 43 depicts the domains. transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 56 kDa that was smaller than the molecular weight of 64,047 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the was similar to Mycobacterium tuberculosis hypothetical protein Rv0235c (Accession No. CAB07001). Table 30 shows the comparison between amino acid sequences

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of the human protein of the present invention (HP) and Mycobacterium tuberculosis hypothetical protein Rv0235c (MT). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 41.7% in the entire region other than the N-terminal region. In addition, the region from alanine at position 293 to proline at position 502 matched with human putative novel protein c360B4.1 (Accession No. CAB56180).

Table 30

HP	MAAPAESLRRRKTGYSDPEPESPPAPGRGPAGSPAHLHTGTFWLTRIVLLKALAFVYFVA
	**. *
МТ	MGWFSAPEYWLGRLALERGTAIIYLIA
HP	FLVAFHQNKQLIGDRGLLPCRVFLKNFQQYFQDRTSWEVFSYMPTILWLMDWSDMNSNLD
	** .* **
МТ	FVAAAQQFRPLIGEHGMLPVPRYLAG-QSFWRTPSIFH-FRYSDRVFAGVCWLGAVLS
HP	LLALLGLGISSFVLITGCANMLLMAALWGLYMSLVNVGHVWYSFGWESQLLETGFLGIFL
• -	* . * . * * . * . *
мт	AAVVAGAASFVPLWATMLIWLTLWVLYLSIVNVGQAWYSFGWESLLLETGFLMIFU

	HP CPLWTLSRLPQHTPTSRIVLWGFRWLIFRIMLGAGLIKIRGDRCWRDLTCMDFHYETQPM
	.* * * * * * * * * * * * * * * * * * *
	MT GNERTAPPILTLLLA-RWLLFRVEFGAGLIKMRGDSCWRSLTCLYYHHETQPM
5	
	HP PNPVAYYLHHSPWWFHRFETLSNHFIELLVPFFLFLGRRACIIHGVLQILFQAVLIVSGN
	*.*** * .**.**** *** * * ***
	MT PGPLSWFFHHLPKPLHRIEVAGNHFAQLVVPFGLFTPQPAASIAAAIIVVTQLWLVASGN
	· · · · · · · · · · · · · · · · · · ·
10	HP LSFLNWLTMVPSLACFDDATLGFLFPSGPGSLKDRVLQMQRDIRGARPEPRFGSVVRRAA
	·*·****·· *** ···· ·* ···* ···* · · · ·
	MT FSWLNWLTILLACSAIDTSS-AAALLPMPAQPALSAPPQWFAGLVV
	.  HP NVSLGVLLAWLSVPVVLNLLSSRQVMNTHFNSLHIVNTYGAFGSITKERAEVILQGTASS
15	*** ** . ***** * ** ** . * ******* * ** ** *
	MT VFTAAVLLLSYWPARNLLSSHQRMNMSFNPFHLVNTYGAFGSICRTRREVVIEGTDES
	HP NASAPDAMWEDYEFKCKPGDPSRRPCLISPYHYRLDWLMWFAAFQTYEHNDWIIHLAGKL
	* . * * * * * * * * * * * * *
20	MT:-PITEQTVWKAYEFKGKPGDPRRLPRQWAPYHLRLDWLMWFAAISPGYALPWMTPFLNRL:
	HP LASDAEALSLLAHNPFAGRPPPRWVRGEHYRYKFSRPGGRHAAEGKWWVRKRIGAYFPPL
	* * * * * * * * * * * * * * * * * * * *
	MT LRNDPATLKLLRHNPFP-QSPPRYVRAQLYQYRFTTVAELRRDRA-WWHRTLIGRYVPPM
25	to a serious and a serious contraction of the serious serious serious serious serious and the serious serious

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HP SLEELRPYFRDRGWPLPGPL

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MT SLRKVASPPAD

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA019047) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03877> (SEQ ID NOS: 124, 134 and 144)

Determination of the whole base sequence of the cDNA insert of clone HP03877 obtained from cDNA library of human kidney revealed the structure consisting of a 106-bp 5'-untranslated region, a 1221-bp ORF, and a 678-bp 3'untranslated region. The ORF encodes a protein consisting of 406 amino acid residues and there existed four putative transmembrane domains. Figure 44 depicts ... the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 49 kDa that was somewhat larger than the molecular weight of 46,208 predicted from the ORF.

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The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Caenorhabditis elegans hypothetical protein Y37D8A (Accession No. CAA21543). Table 31 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Caenorhabditis elegans hypothetical protein Y37D8A (CE). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 50.2% in the intermediate region of 329 amino acid residues.

15 Table 31

HP MAENG

CE MAKKOKKSTEKSERTVEFKEPPKPANSEERLVSTRQFLAKIGQKKLIKKKVKNFRFSKKT

HP KNCDQRRVAMNKEHHNGNFTDPSSVNEKKRREREERQNIVLWRQPLITLQYFSLEILVIL

CE FIDFFSENQKKNCRLKPAGRGMKPSPSQNTLNRMERETIVFWRRPHIVIPYALMEIAHLA

25 HP KEWTSKLWHRQSIVVSFLLLLAVLIATYYVEGVHQQYVQRIEKQFLLYAYWIGLGILSSV 25

1D	GLGTGLHTFLLYLGPHIASVTLAAYECNSVNFPEPPYPDQIICPDEEGTEGTISLWSIIS
ш	*** ***** ***** ** ** ** ** ** * * ** *
CE	GLGSGLHTFLIYLGPHIAAVTMAAYECQSLDFPQPPYPESIQCPSTKSSI-AVTFWQIVA
iΡ	KVRIEACMWGIGTAIGELPPYFMARAARLSGAEPDDEEYQEFEEMLEHAESAQDFA-
	***.*** ***. *************. ** *
Œ	KVRVESLLWGAGTALGELPPYFMARAARISGQEPDDEEYREFLELMNADKESDADQKLSI
ŧΡ	-SRAKLAVQKLVQKVGFFGILACASIPNPLFDLAGITCGHFLVPFWTFFGATLIGKAIIK
	.*** *** *** *********************
Œ.	VERAKSWVEHNIHRLGFPGILLFASIPNPLFDLAGITCGHFLVPFWSFFGATLIGKALVK
ΙP	MHIQKIFVIITFSKHIVEQMVAFIGAVPGIGPSLQKPFQEYLEAQRQKLHHKSEMGTPQG
	**. *. ***. **. *
CE	MHVQMGFVILAFSDHHAENFVKILEKIPAVGPYIRQPISDLLEKQRKALHKTPGEHSEQD
łР	ENWLSWMFEKLVVVMVCYFILSIINSMAQSYAKRIQQRLNSEEKTK
CE	LIDEENQSFEEEEEAVTPPSSCPLLLSDGFEGVVVKK

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of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T18977) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10765> (SEQ ID NOS: 125, 135 and 145)

Determination of the whole base sequence of the CDNA insert of clone HP10765 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 30-bp 5'-untranslated region, a 1362-bp ORF, and a 166-bp 3'-untranslated region. The ORF encodes a protein consisting of 453 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 45 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 48 kDa that was almost identical with the molecular weight of 47,724 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI792834) among ESTs. However, since they are partial sequences, it can not be judged whether or not they

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encode the same protein as the protein of the present invention.

<HP10766> (SEQ ID NOS: 126, 136 and 146)

Determination of the whole base sequence of the cDNA insert of clone HP10766 obtained from cDNA library of human kidney revealed the structure consisting of a 150-bp 5'-untranslated region, a 180-bp ORF, and a 675-bp 3'untranslated region. The ORF encodes a protein consisting of 59 amino acid residues and there existed two putative transmembrane domains. Figure 46 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 10 kDa or less that was almost identical with the molecular weight of 6,098 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T85491) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10770> (SEQ ID NOS: 127, 137 and 147)

Determination of the whole base sequence of the cDNA insert of clone HP10770 obtained from cDNA library of

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human kidney revealed the structure consisting of a 150-bp 5'-untranslated region, a 633-bp ORF, and a 186-bp 3'-untranslated region. The ORF encodes a protein consisting of 210 amino acid residues and there existed two putative transmembrane domains. Figure 47 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was larger than the molecular weight of 22,156 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI792771) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10772> (SEQ ID NOS: 128, 138 and 148) =

Determination of the whole base sequence of the cDNA insert of clone HP10772 obtained from cDNA library of human kidney revealed the structure consisting of a 19-bp 5'-untranslated region, a 498-bp ORF, and a 724-bp 3'-untranslated region. The ORF encodes a protein consisting of 165 amino acid residues and there existed four putative transmembrane domains. Figure 48 depicts the

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hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. F11871) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10773> (SEQ ID NOS: 129, 139 and 149)

Determination of the whole base sequence of the cDNA insert of clone HP10773 obtained from cDNA library of human kidney revealed the structure consisting of a 186-bp 5'-untranslated region, a 489-bp ORF, and a 499-bp 3'untranslated region. The ORF encodes a protein consisting of 162 amino acid residues and there existed four putative transmembrane domains. Figure 49 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of

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sequences that shared a homology of 90% or more (for example, Accession No. N33828) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10776> (SEQ ID NOS: 130, 140 and 150) /

Determination of the whole base sequence of the cDNA insert of clone HP10776 obtained from cDNA library of human kidney revealed the structure consisting of a 207-bp 5'-untranslated region, a 666-bp ORF, and a 139-bp 3'-untranslated region. The ORF encodes a protein consisting of 221 amino acid residues and there existed three putative transmembrane domains. Figure 50 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 30 kDa that was larger than the molecular weight of 24,883 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI929639) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

## INDUSTRIAL APPLICABILITY

The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, 5 expression vectors for these DNAs and eukaryotic cells expressing these DNAs. Since all of the proteins of the present invention are secreted or exist in the cell membrane, they are considered to be proteins controlling proliferation and/or the differentiation of the cells. 10 Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents control the proliferation and/or differentiation of the cells, or as antigens for preparing antibodies against these proteins. The DNAs of the present 15 invention can be utilized as probes for the genetic diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for expressing these proteins in large quantities. Cells into which these genes introduced to express these proteins can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibody of the present invention can be utilized for the detection, quantification, purification and the like of the protein of the present invention.

25 The present invention also provides genes

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corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons; introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or information sequence the disclosed from primers identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254;

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Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA. 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination,

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preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the identified in accordance with known invention can be techniques for determination of such domains from sequence information.

proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed

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protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is,

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naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

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Table 32

Stringency	Poly-	Hybrid	Hybridization Temperature	Wash
Condition	nucleotide	Length	and Buffer	Temperature
	Hybrid	(bp) *		and Buffer
A	DNA: DNA	≥50	65°C; 1×SSC -or-	65°C;
			42°C; 1×SSC,50%	0.3×SSC
			formamide	
В	DNA: DNA	<50	T <sub>8</sub> *; 1×SSC	T <sub>s</sub> *; 1×SSC
С	DNA: RNA	≥50	67°C; 1×SSC -or-	67°C;
			45°C; 1×SSC,50%	0.3×SSC
		4	formamide	
D	DNA: RNA	<50	T <sub>D</sub> *; 1×SSC	Tp*; 1×SSC
E	RNA: RNA	≥50	70°C; 1×SSC -or-	70°C;
			50°C; 1×SSC,50%	0.3×SSC
	· ·	<u> </u>	formamide	
F	RNA: RNA	<50	T <sub>F</sub> *; 1×SSC	T <sub>F</sub> *; 1×SSC
G	DNA: DNA	≥50	65°C; 4×SSC -or-	65°C; 1×SSC
			42°C; 4×SSC,50%	
			formamide	
. Н	DNA: DNA	<50	T <sub>H</sub> *; 4×SSC	T <sub>H</sub> *; 4×SSC
I	DNA: RNA	≥50	67°C; 4×SSC -or-	67°C; 1×SSC
		_	45°C; 4×SSC,50%	
			formamide	
J	DNA: RNA	<b>.&lt;50</b>	T <sub>J</sub> *; 4×SSC	T <sub>J</sub> *; 4×SSC
K.	RNA: RNA	≥50	70°C; 4×SSC -or-	67°C; 1×SSC
			50°C; 4×SSC,50%	ļ
			formamide	
L	RNA: RNA	<b>&lt;</b> 50 .	T <sub>L</sub> *; 2×SSC	T <sub>L</sub> *; 2×SSC
М	DNA: DNA	≥50	50°C; 4×SSC -or-	50°C; 2×SSC
[			40°C; 6×SSC,50%	·
			formamide	
. N	DNA: DNA	<50	T <sub>N</sub> *; 6×SSC	T <sub>N</sub> *; 6×SSC
0	DNA: RNA	≥50	55°C; 4×SSC -or-	55°C; 2×SSC
			42°C; 6×SSC,50%	
			formamide	
P	DNA: RNA	<50	T <sub>p</sub> *; 6×SSC	Tp*; 6×SSC
Q	RNA: RNA	≥50	60°C; 4×SSC -or-	60°C; 2×SSC
	,		45°C; 6×SSC,50%	·
			formamide	
R	RNA: RNA	<50	T <sub>R</sub> *; 4×SSC	T <sub>R</sub> *; 4×SSC

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- t: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides.

  When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.
- t: SSPE (1×SSPE is 0.15M NaCl, 10mM NaH<sub>2</sub>PO<sub>4</sub>, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.
- 15  $*T_B T_R$ : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature  $(T_m)$  of the hybrid, where  $T_m$  is determined according to the following equations. For hybrids less than 18 base pairs in length,  $T_m(^{\circ}C) = 2 (\#of A + T bases) + 4 (\# of G + C bases)$ . For hybrids between 18 and 49 base pairs in length,  $T_m(^{\circ}C) = 81.5 + 16.6 (log_{10}[Na^{\dagger}]) + 0.41 (\%G+C) (600/N)$ , where N is the number of bases in the hybrid, and  $[Na^{\dagger}]$  is the concentration of sodium ions in the hybridization buffer  $([Na^{\dagger}])$  for  $1 \times SSC = 0.165M$ .

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Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

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## CLAIMS

- 1. A protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130.
- 2. An isolated DNA encoding the protein according to Claim 1.
- 3. An isolated cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS:

  10 11 to 20, 41 to 50, 71 to 80, 101 to 110 and 131 to 140.
  - 4. The cDNA according to Claim 3 consisting of any one of a base sequence selected from the group consisting of SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120 and 141 to 150.
- 5. An expression vector that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 by in vitro translation or in eukaryotic cells.
  - 6. A transformed eukaryotic cell that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 and of producing the protein according to Claim 1.
  - 7. An antibody directed to the protein according to Claim 1.

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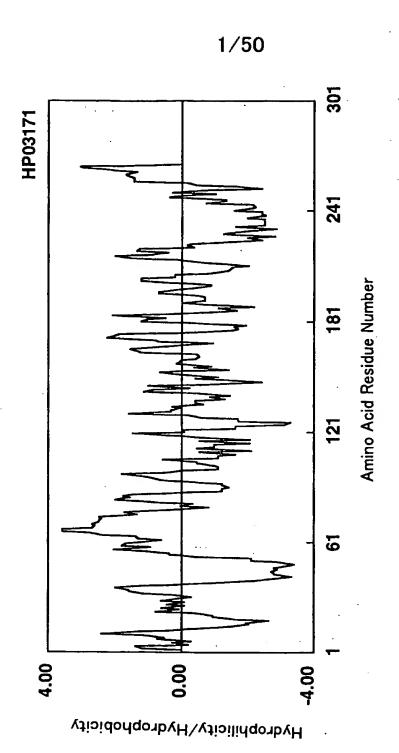
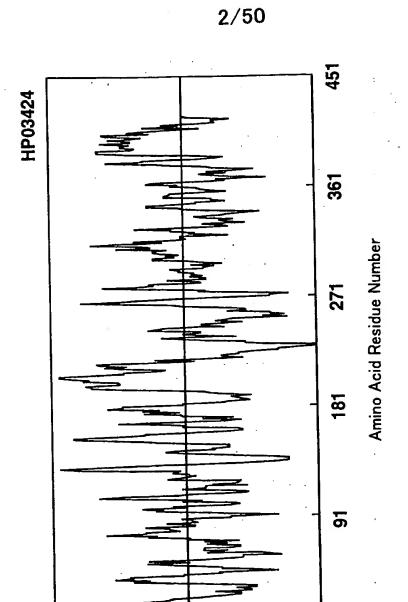


Fig.1

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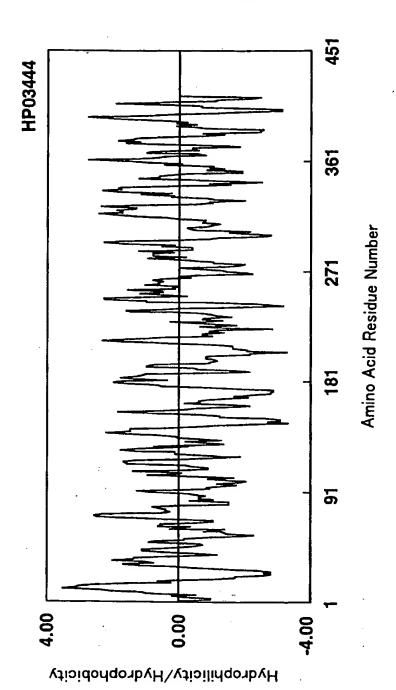
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Fig.2

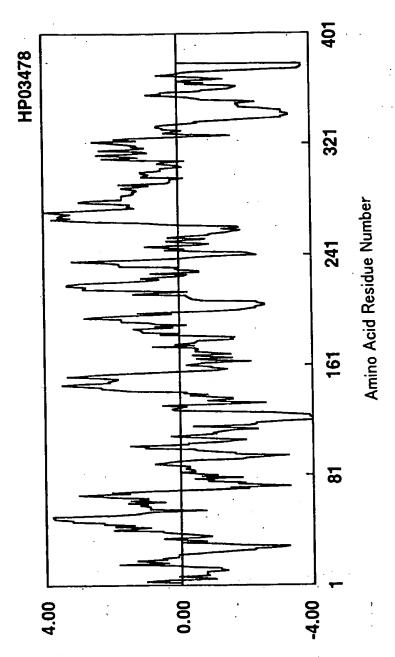
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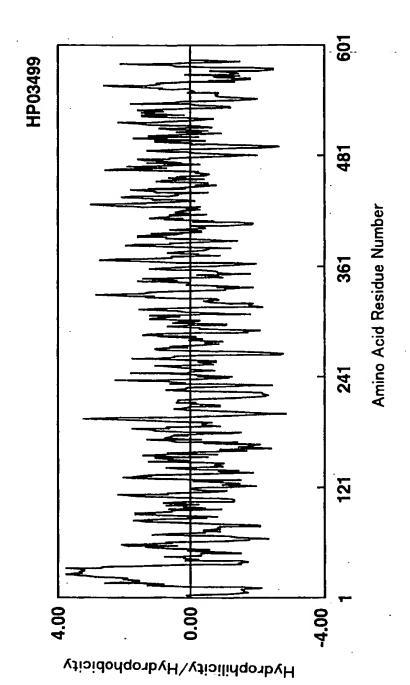
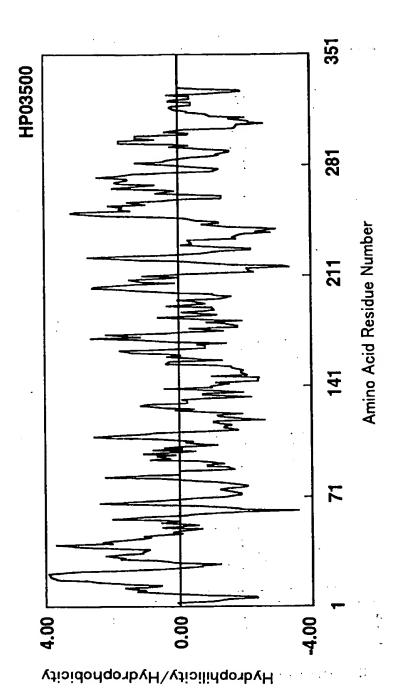


Fig.5





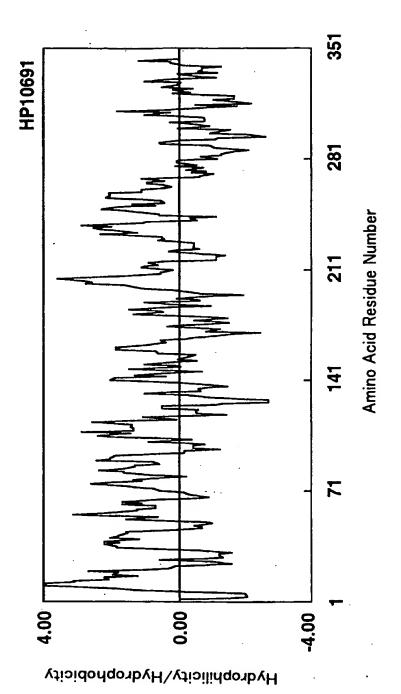
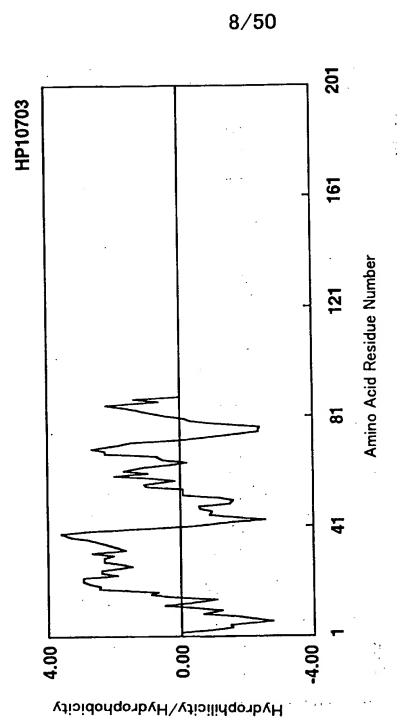


Fig.7

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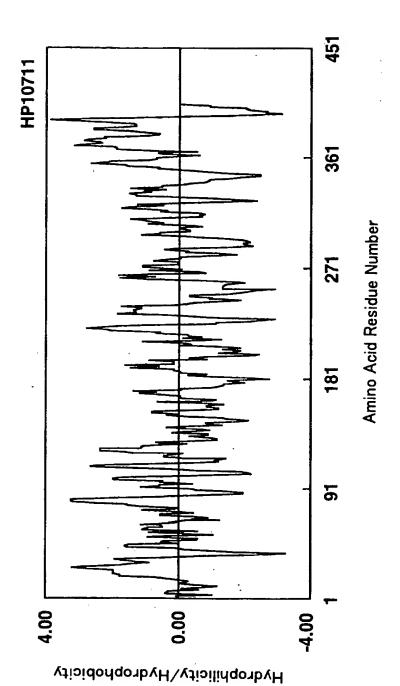
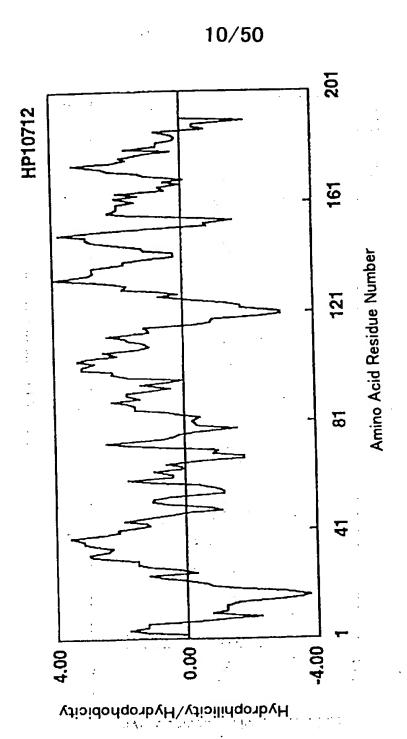


Fig.9

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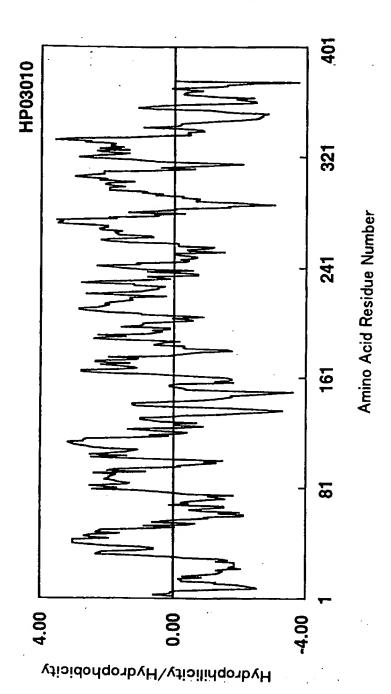


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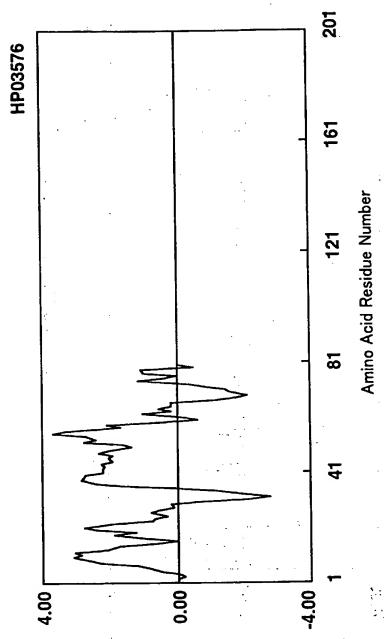
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Hydrophilicity/Hydrophobicity

Fig. 12

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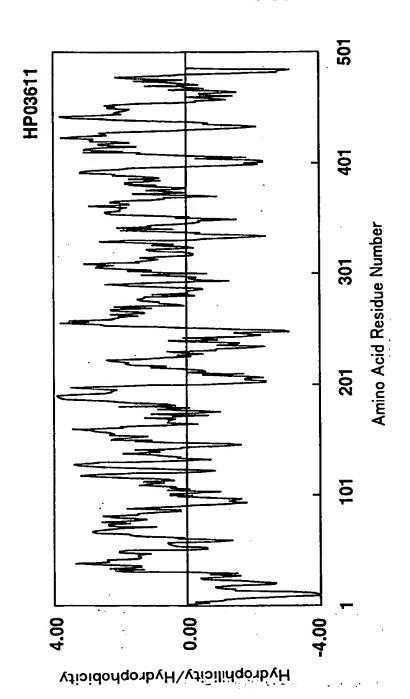


Fig.13



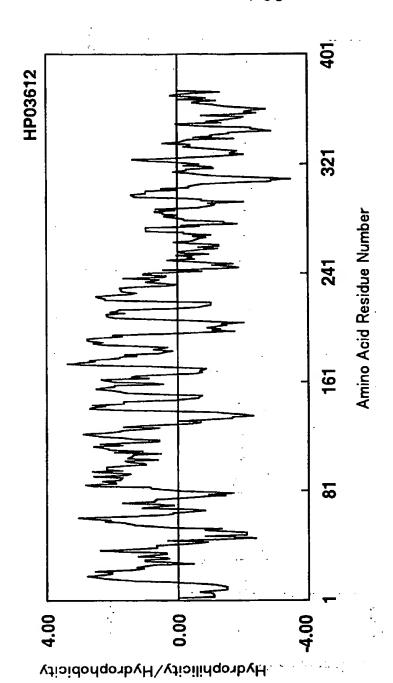


Fig.14



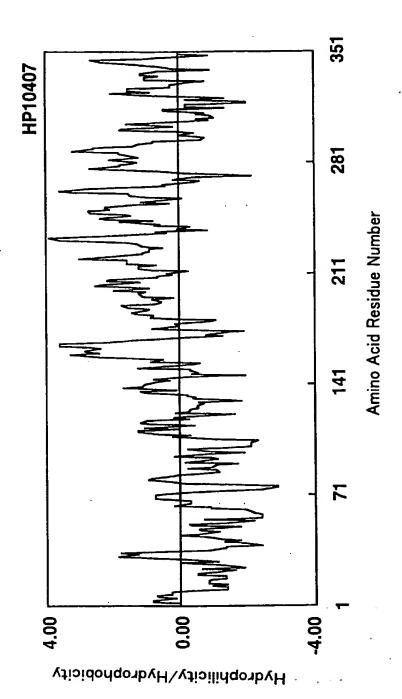


Fig. 15

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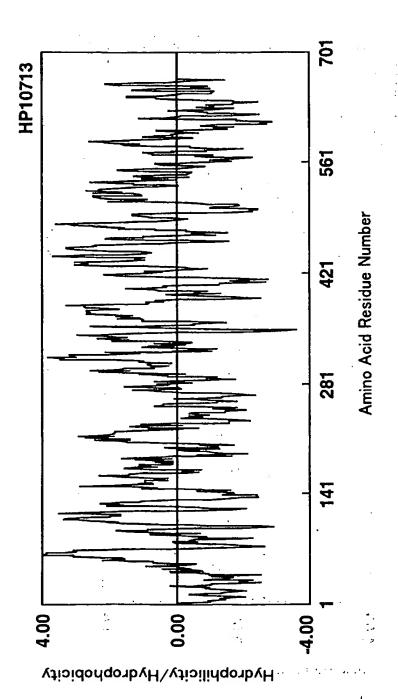
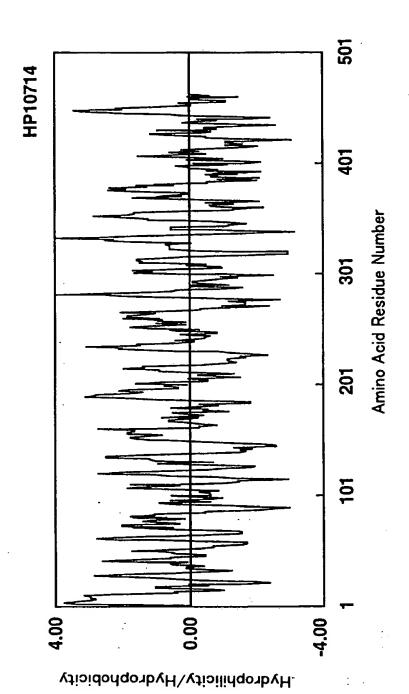


Fig.16

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BNSDOCID: WO 011366042 L >





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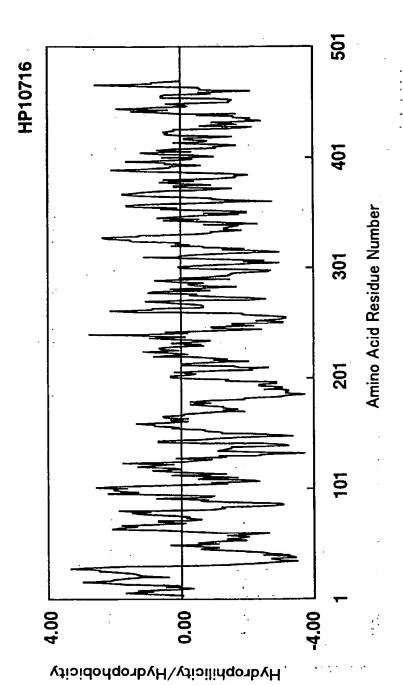


Fig. 18

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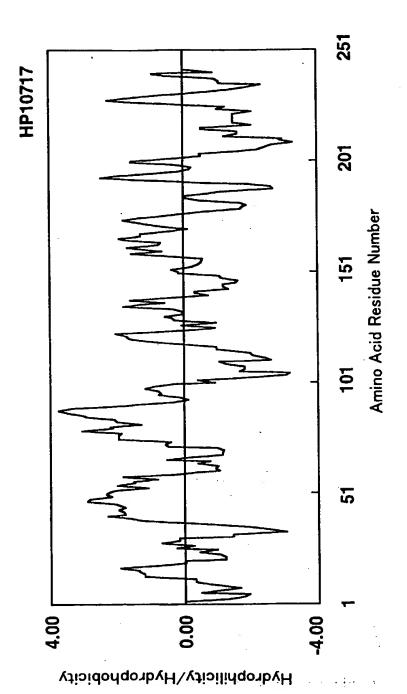
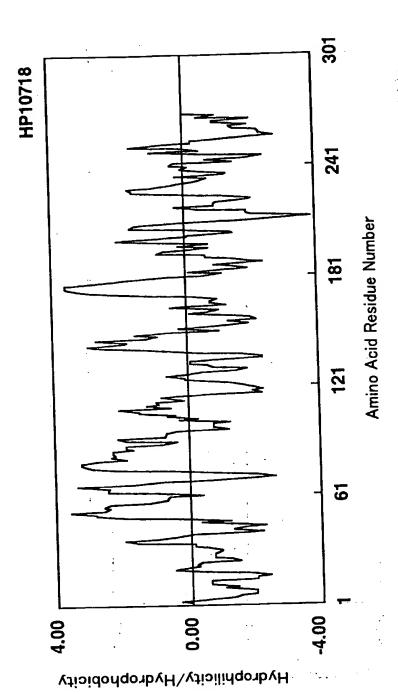


Fig. 19

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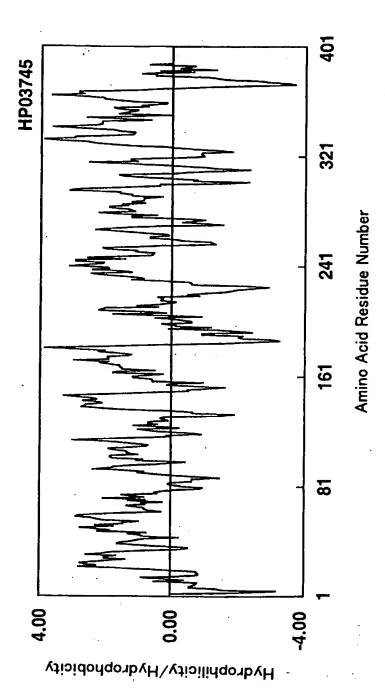


Fig.21

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. . .

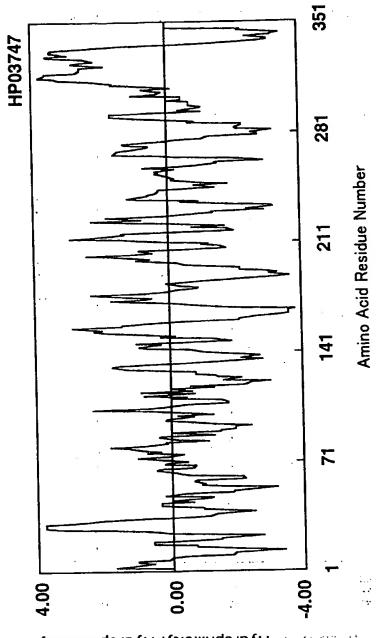


Fig.22

Hydrophilicity/Hydrophobicity

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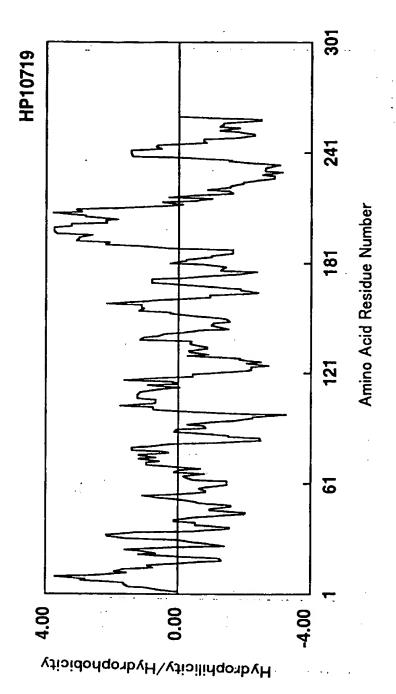


Fig. 23



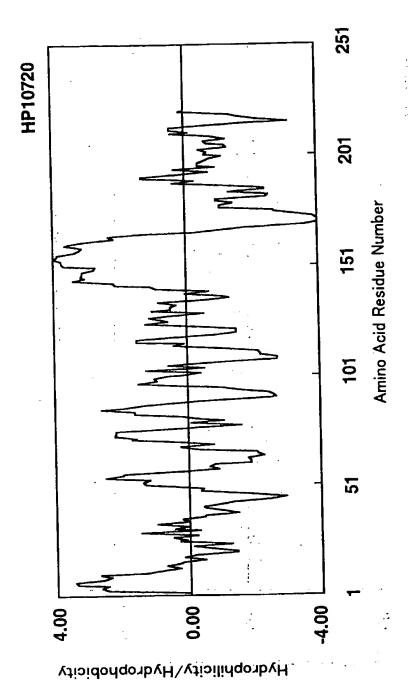


Fig.24



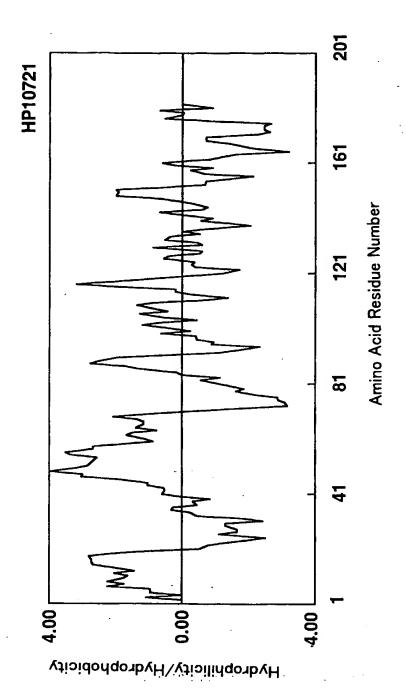


Fig. 25

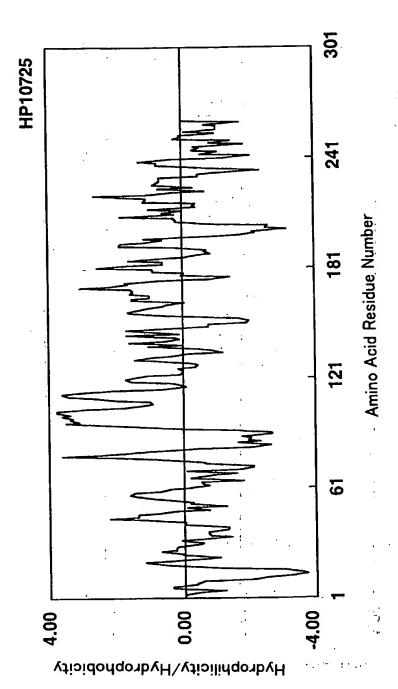
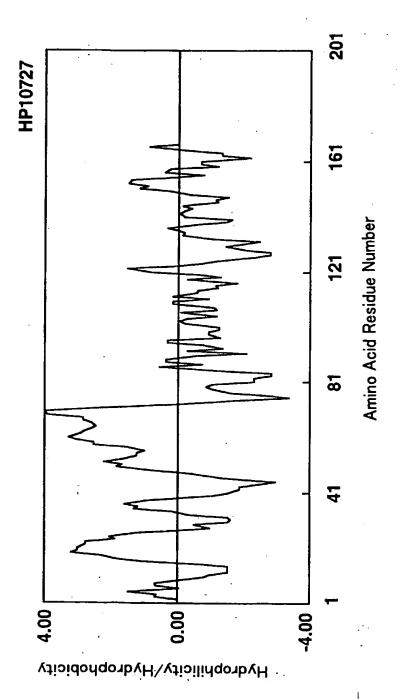
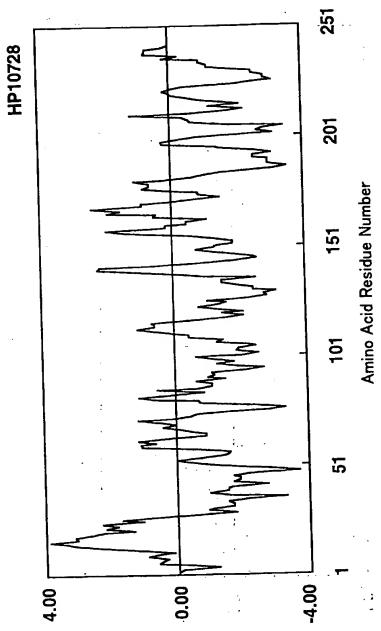


Fig.26

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Hydrophilicity/Hydrophobicity.

Fig.28

PNSDOCID: <WO 0112660A2 I

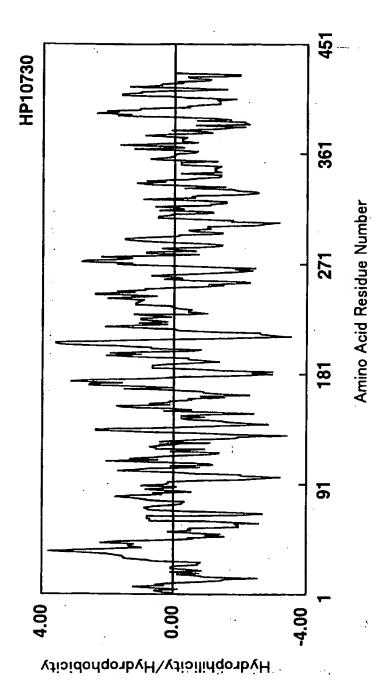


Fig.29

BNSDOCID: -WO -----

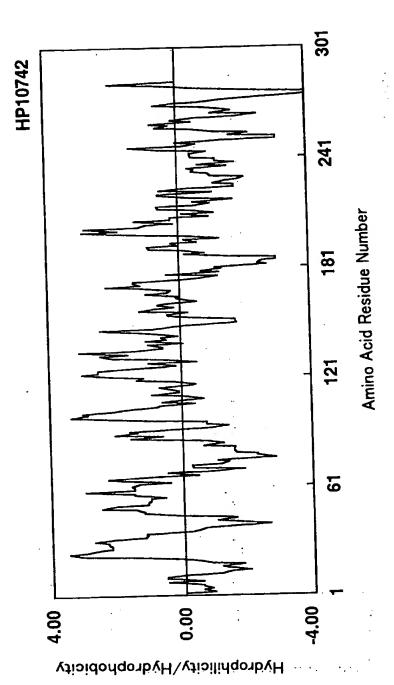
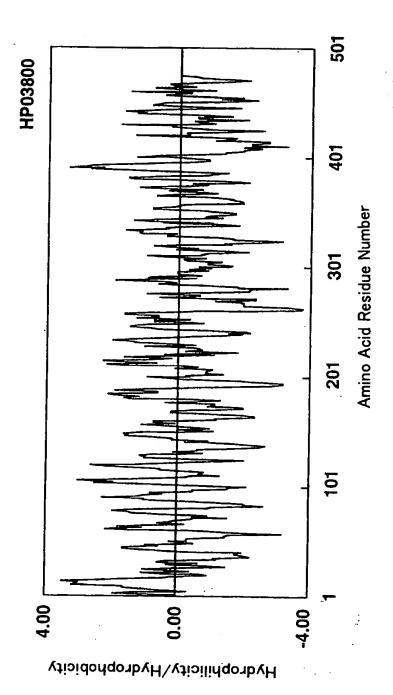
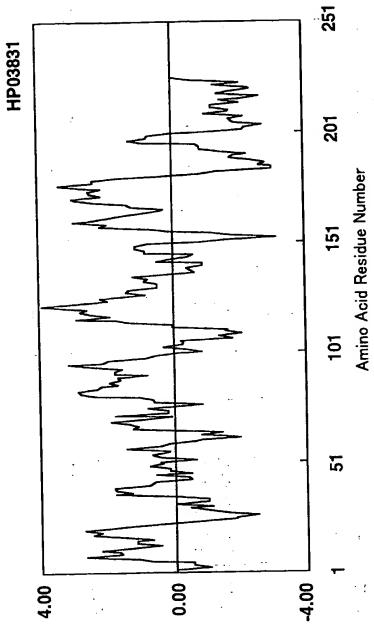


Fig.30

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-ig.32

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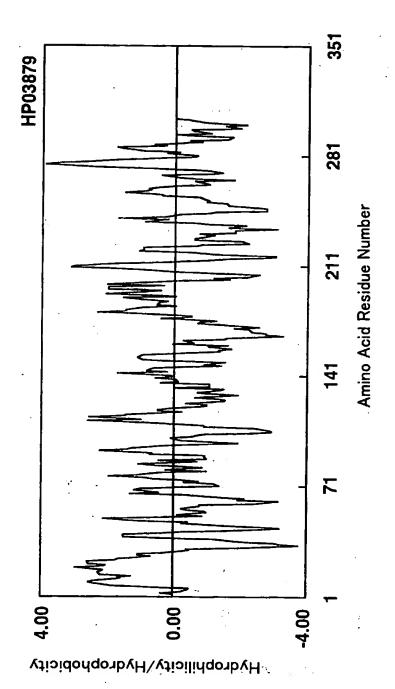


Fig.33

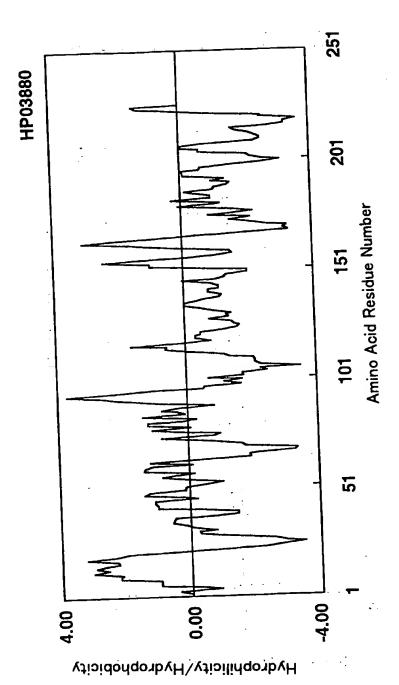
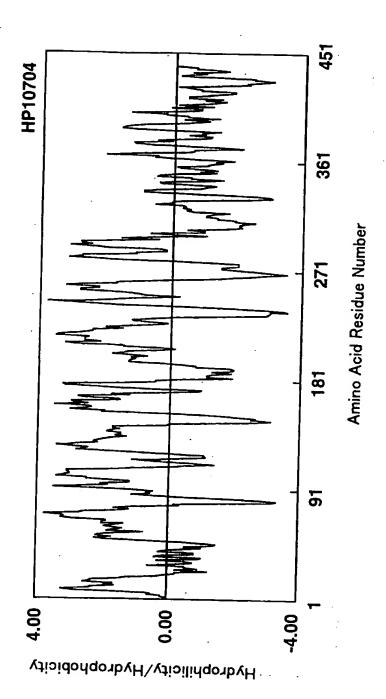


Fig.34

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-ig.35

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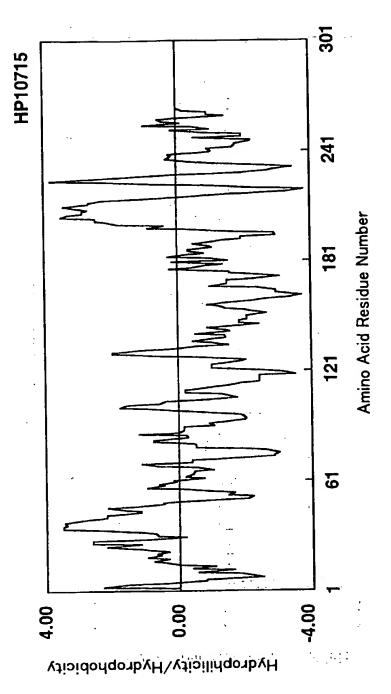


Fig.36

BNSDOCIO - WO 011266082 I S

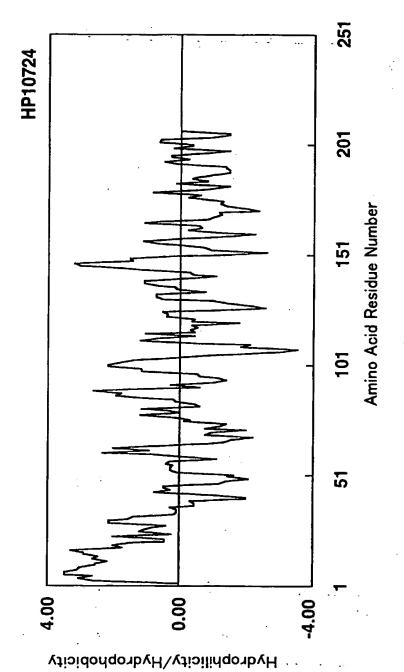
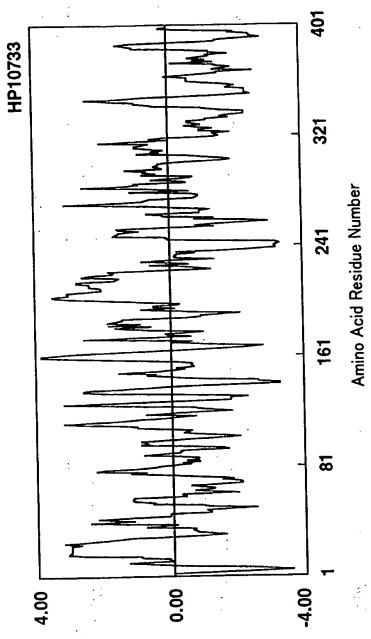


Fig. 37

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Hydrophilicity/Hydrophobicity

Fig.38

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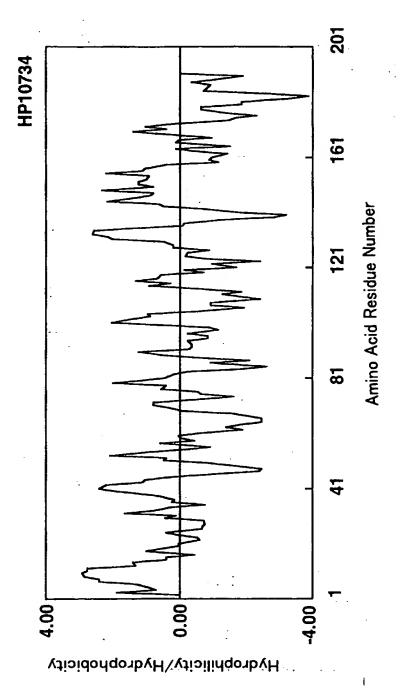


Fig.39

BNSDOCID- -WO 0112660A2 I -

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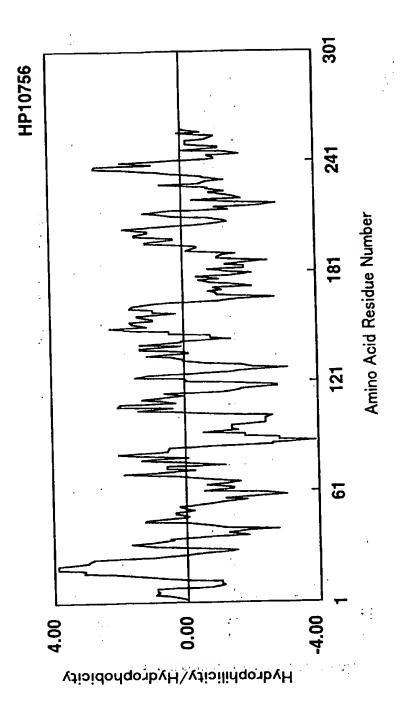
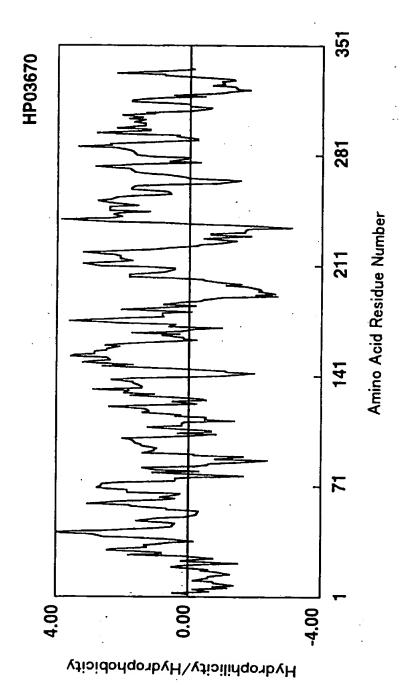
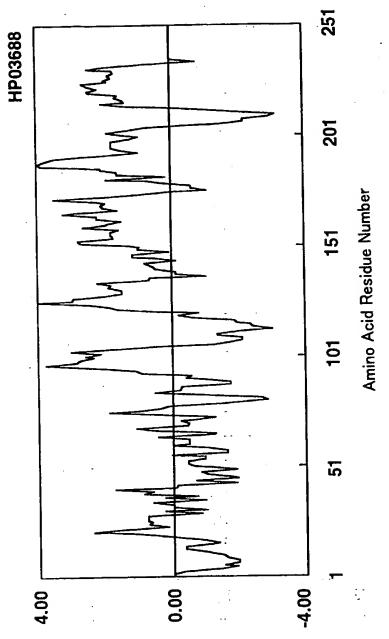


Fig. 40



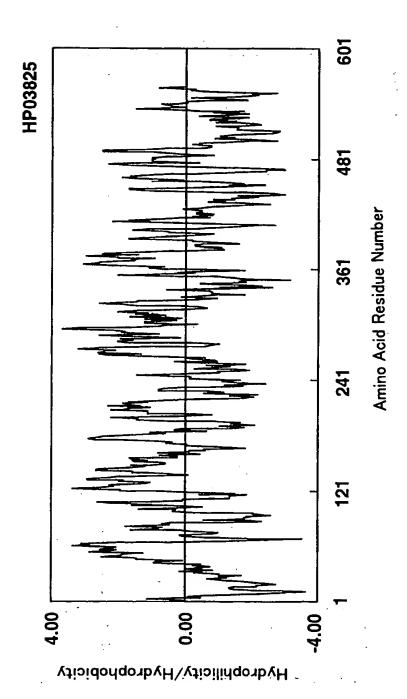
-ig.41



Hydrophilicity/Hydrophobicity

Fig.42





-ig.43

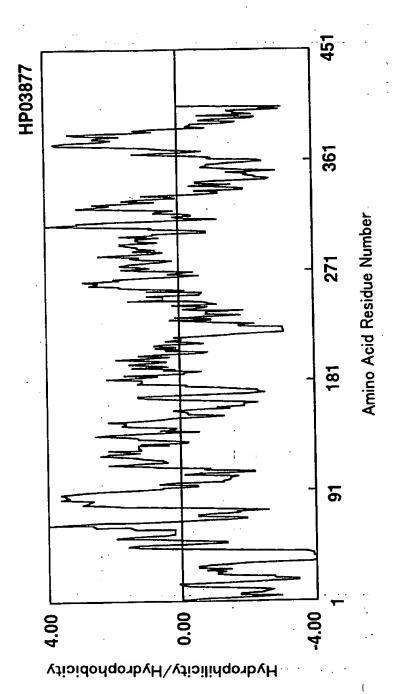


Fig.44

BNSDOCID <WO 0112660A2 1 >

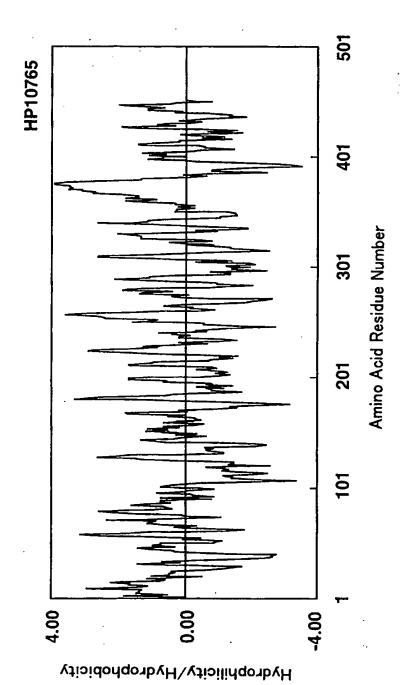
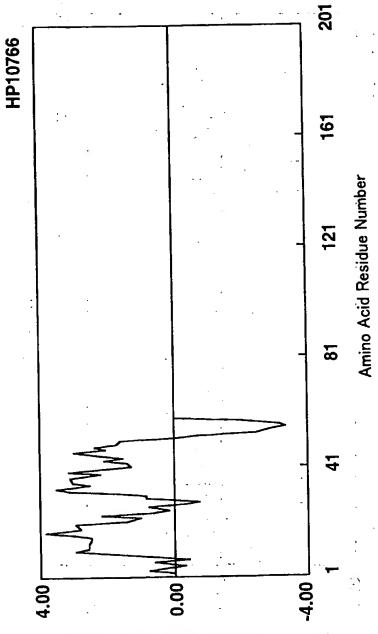


Fig. 45



Hydrophilicity/Hydrophobicity

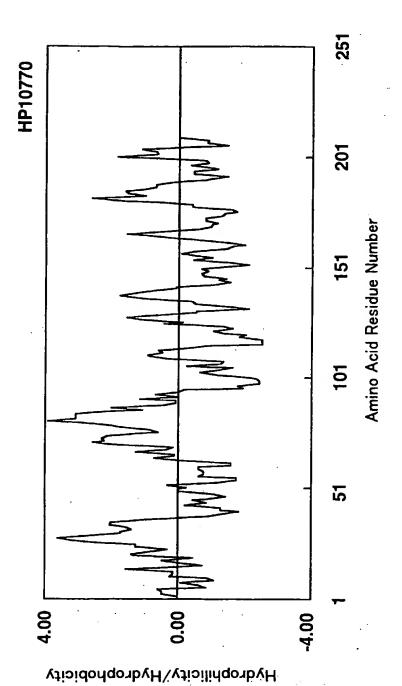
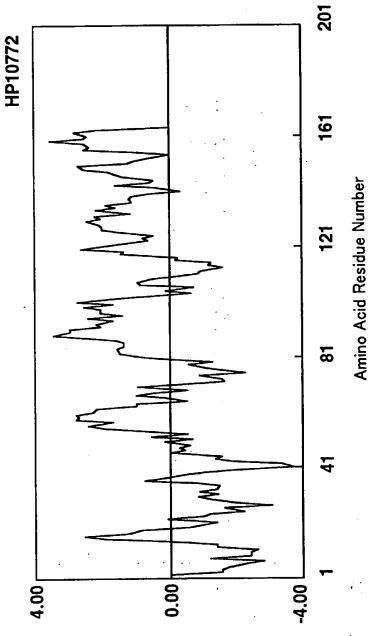


Fig 4

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Hydrophilicity/Hydrophobicity

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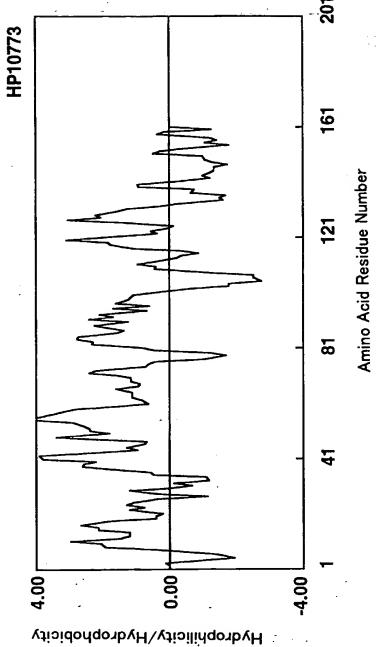
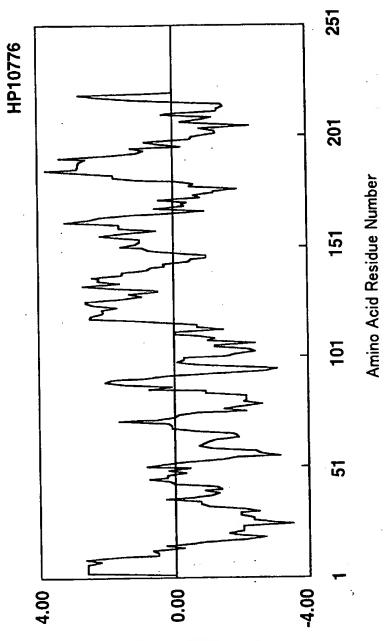


Fig. 49

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Fig.50

BNSDDCID->WO 0112660A2 L>

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#### 1 /307

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140

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Gl	ı Trp	Phe			· ·			-						. ,•	

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Phe	Leu	Ile	· Val	Arg	Tyr	Phe	Phe	Glu	Leu	Tyr	Val	Ala	Thr	Pro	Leu
+	50					55					60				
Ala	Ala	Leu	Leu	ı Asn	Ile	Lys	Glu	Lys	Thr	Arg	Leu	Arg	Ala	Pro	Pro
65	;		•		70	· ·				75	1	٠. ٠,		٠.	∵80
Asr	Ala	Thr	. Let	ı Glu	ı His	Phe	Tyr	Leu	Thr	Ser	Gly	Lys	Gln	Pro	Lys

				85		•			90					95	
G1n	Val	Glu	Val	Glu	Leu	Leu	Ser	Arg	Gln	Ser	Gly	Leu	Ser	Ģly	Arg
			100		. *			105					110		
Gln	Val	Glu	Arg	Trp	Phe	Arg	Arg	Arg	Arg	Asn	Gln	Asp	Arg	Pro	Ser
		115					120					125			
Leu	Leu	Lys	Lys	Phe	Arg	Glu	Ala	Ser	Trp	Arg	Phe	Thr	Phe	Tyr	Leu
	130					135		7 0			140				· ·
Ile	Ala	Phe	Ile	Ala	Gly	Met	Ala	Val	Ile	Val	Asp	Lys	Pro	Trp	Phe
145					150					155					160
Tyr	Asp	Met	Lys	Lys	Val	Trp	Glu	Gly	Tyr	Pro	Ile	Gln	Ser	Thr	Ile
				165					170					175	
Pro	Ser	Gln	Tyr	Trp	Tyr	Tyr	Met	Ile	Glu	Leu	Ser	Phe	Tyr	Trp	Ser
			180					185					190		
Leu	Leu	Phe	Ser	Ile	Ala	Ser	Asp	Val	Lys	Arg	Lys	Asp	Phe	Lys	Glu
		195					200					205			
Gln	Ile	Ile	His	His	Val	Ala	Thr	Ile	Ile	Leu	Ile	Ser	Phe	Ser	Trp
	210					215					220				
Phe	Ala	Asn	Tyr	Ile	Arg	Ala	Gly	Thr	Leu	Ile	Met	Ala	Leu	His	Asp
225	٠,				230					235					240
Ser	Ser	Asp	Tyr	Leu	Leu	Glu	Ser	Ala	Lys	Met	Phe	Asn	Tyr	Ala	Gly
٠.			;	245					250		٠.		٠.	255	
Trp	Lys	Asn	Thr	Cys	Asn	Asn	Ile	Phe	Ile	Val	Phe	Ala	Ile	Val	Phe
۲,		٠.	260			٠,,	٠.	265	•		. •		270		. :
Ile	Ile	Thr	Arg	Leu	Val	Ile	Leu	Pro	Phe	Trp	Ile	Leu	His	Cys	Thr
1.71	. :	275	: '				280			.*		285	_	; .	

Leu Val Tyr Pro Leu Glu Leu Tyr Pro Ala Phe Phe Gly Tyr Tyr Phe 300 290 295 Phe Asn Ser Met Met Gly Val Leu Gln Leu Leu His Ile Phe Trp Ala 315 310 Tyr Leu Ile Leu Arg Met Ala His Lys Phe Ile Thr Gly Lys Leu Val 330 335 325 Glu Asp Glu Arg Ser Asp Arg Glu Glu Thr Glu Ser Ser Glu Gly Glu 340 345 350 Glu Ala Ala Gly Gly Gly Ala Lys Ser Arg Pro Leu Ala Asn Gly 355 360 365 His Pro Ile Leu Asn Asn Asn His Arg Lys Asn Asp 380 370 375 <210> 5 <211> 585 <212> PRT \* <213> Homo sapiens **<400> 5** Met Val Cys Arg Glu Gln Leu Ser Lys Asn Gln Val Lys Trp Val Phe 1 5 10 15 Ala Gly Ile Thr Cys Val Ser Val Val Val Ile Ala Ala Ile Val Leu 20 25 30 Ala Ile Thr Leu Arg Arg Pro Gly Cys Glu Leu Glu Ala Cys Ser Pro 45 35 40 Asp Ala Asp Met Leu Asp Tyr Leu Leu Ser Leu Gly Gln Ile Ser Arg

	50					55					60			٠	
Arg	Asp	Ala	Leu	Glu	Val	Thr	Trp	Tyr	His	Ala	Ala	Asn	Ser	Lys	Lys
65					70					.75					80
Ala	Met	Thr	Ala	Ala	Leu	Asn	Ser	Asn	Ile	Thr	Val	Leu	Glu	Ala	Asp
	•			85					90					95	
Val	Asn	Val	Glu	Gly	Leu	Gly	Thr	Ala	Asn	Glu	Thr	Gly	Val	Pro	Ile
			100					105				í	110		
Met	Ala	His	Pro	Pro	Thr	Ile	Tyr	Ser	Asp	Asn	Thr	Leu	Glu	Gln	Trp
		115					120					125			
Leu	Asp	Ala	Val	Leu	Gly	Ser	Ser	Gln	Lys	Gly	Ile	Lys	Leu	Asp	Phe
	130					135					140				
Lys	Asn	Ile	Lys	Ala	Val	Gly	Pro	Ser	Leu	Asp	Leu	Leụ	Arg	Gln	Leu
145					150					155					160
Thr	Glu	Glu	Gly	Lys	Val	Arg	Arg	Pro	Ile	Trp	Ile	Asn	Ala	Asp	Ile
				165					170					175	
Leu	Lys	Gly	Pro	Asn	Met	Leu	Ile	Ser	Thr	Glu	Val	Asn	Ala	Thr	Gln
			180					185					190		
Phe	Leu	Ala	Leu	Val	Gln	G1u	Lys	Tyr	Pro	Lys	Ala	Thr	Leu	Ser	Pro
		195					200					205			
Gly	Trp	Thr	Thr	Phe	Tyr	Met	Ser	Thr	Ser	Pro	Asn	Arg	Thr	Tyr	Thr
••	210	*		•		215					220				;
Gln	Ala	Met	Val	Glu	Lys	Met	His	Glu	Leu	Val	Gly	Gly	Val	Pro	Gln
225			×	•	230		ï ,i.	, . · .	,	235	: .	•	e •	:	240
Arg	Val	Thr	Phe	Pro	Val	Arg	Ser	Ser	Met	Val	Arg	Ala	Ala	Trp	Pro
t .	,		٠,	245				σ.,	250					255	

His	Phe	Ser	Trp	Leu	Leu	Ser	Gln	Ser	Glu	Arg	Tyr	Ser	Leu	Thr	Leu
	•		260				-	265				•	270	•	· 5
Trp	Gln	Ala	Ala	Ser	Asp	Pro	Met	Ser	Val	Glu	Asp	Leu	Leu	Tyr	Val
		275	,				280					285			
Arg	Asp	Asn	Thr	Ala	Val	His	Gln	Val	Tyr	Tyr	Asp	Ile	Phe	Glu	Pro
	290					295	٠.		•		300			•	. 1
Leu	Leu	Ser	Gln	Phe	Lys	Gln	Leu	Ala	Leu	Asn	Ala	Thr	Arg	Lys	Pro
305		ر			310					315		•			320
Met	Tyr	Tyr	Thr	Gly	Gly	Ser	Leu	Ile	Pro	Leu	Leu	G1n	Leu	Pro	Gly
•				325	0				330					335	
Asp	Asp	Gly	Leu	Asn	Val	Glu	Trp	Leu	Val	Pro	Asp	Val	Gln	Gly	Ser
		, .	340				•	345	- 1		:	÷ -	350		·)(· • .
Gly	Lys	Thr	Ala	Thr	Met	Thr	Leu	Pro	Asp	Thr	Glu	Gly	Met	Ile	Leu
	··· .	355					360					365			
Leu	Asn	Thr	Gly	Leu	Glu	Gly	Thr	Val	Ala	Glu	Asn	Pro	Val	Pro	Ile
	370					375					380				
Val	His	Thr	Pro	Ser	Gly	Asn	Ile	Leu	Thr	Leu	Glu	Ser	Cys	Leu	G1n
385	;				390		,			395					400
Gln	Leu	Ala	Thr	His	Pro	G1y	His	Trp	Gly	Ile	His	Leu	G1n	Ile	Ala
				405	i			.  +	410			٠		415	
Glu	ı Pro	Ala	ı Ala	Leu	Arg	Pro	Ser	Leu	Ala	Leu	Leu	Ala	Arg	Leu	Ser
			420	)			-	425	i				430	ÿ	
Sei	r Leu	ı Gly	/ Leu	ı Lev	ı His	Trp	Pro	Val	Trp	Val	Gly	Ala	Lys	: Ile	Ser
															ea.
н	s G1s	i Sei	r Pha	e Ser	· Val	Pro	Glv	, His	; Val	Ala	G1v	Ars	g Glu	ı Let	ı Leu

450 455 460
Thr Ala Val Ala Glu Val Phe Pro His Val Thr Val Ala Pro Gly Trp
465 470 475 480
Pro Glu Glu Val Leu Gly Ser Gly Tyr Arg Glu Gln Leu Leu Thr Asp
485 490 495
Met Leu Glu Leu Cys Gln Gly Leu Trp Gln Pro Val Ser Phe Gln Met
500 505 510
Gln Ala Met Leu Leu Gly His Ser Thr Ala Gly Ala Ile Gly Arg Leu
515 520 525
Leu Ala Ser Ser Pro Arg Ala Thr Val Thr Val Glu His Asn Pro Ala
530 535 540
Gly Gly Asp Tyr Ala Ser Val Arg Thr Ala Leu Leu Ala Ala Arg Ala
545 550 555 560
Val Asp Arg Thr Arg Val Tyr Tyr Arg Leu Pro Gln Gly Tyr His Lys
565 570 575
Asp Leu Leu Ala His Val Gly Arg Asn
580 585
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<211> 331
<212> PRT
<213> Homo sapiens
<b>⟨400⟩ 6</b> •
Met Trp Leu Trp Glu Asp Gln Gly Gly Leu Leu Gly Pro Phe Ser Phe
(1) 1 1 1 1 1 1 1 1 1 1 1 5 1 1 1 1 1 5 1

Leu	Leu	Leu	Val	Leu	Leu	Leu	Val	Thr	Arg	Ser	Pro	Val	Asn	Ala	Cys
		ı	20	•				25					30		
Leu	Leu	Thr	Gly	Ser	Leu	Phe	Val	Leu	Leu	Arg	Val	Phe	Ser	Phe	Glu
	•	<sup>:.</sup> 35					40					45			
Pro	Val	Pro	Ser	Cys	Arg	Ala	Leu	G1n	Val	Leu	Lys	Pro	Arg	Asp	Arg
	50		•	•		55					60		-		,
Ile	Ser	Ala	Ile	Ala	His	Arg	Gly	Gly	Ser	His	Asp	Ala	Pro	Glu	Asn
65					70	•		٠.		75			•	٠.	80
Thr	Leu	Ala	Ala	Ile	Arg	Gln	Ala	Ala	Lys	Asn	Gly	Ala	Thr	Gly	Val
,	• •			85		. •	•		90					95	
Glu	Leu	Asp	Ile	Glu	Phe	Thr	Ser	Asp	Gly	Ile	Pro	Val	Leu	Met	His
	••		100	•				105		•	•		110	•	
Asp	Asn	Thr	Val	Asp	Arg	Thr	Thr	Asp	Gly	Thr	Gly	Arg	Leu	Cys	Asp
		115					120			-		125			
Leu	Thr	Phe	Glu	Gln	Ile	Arg	Lys	Leu	Asn	Pro	Ala	Ala	Asn	His	Arg
	130					135		٠.		•	140				
Leu	Arg	Asn	Asp	Phe	Pro	Asp	Glu	Lys	Ile	Pro	Thr	Leu	Arg	Glu	Ala
145					150					155					160
Val	Ala	Glu	Cys	Leu	Asn	His	Asn	Leu	Ţhr	Ile	Phe	Phe	Asp	Val	Lys
				165					170					175	•
Gly	His	Ala	His	Lys	Ala	Thr	Glu	Ala	Leu	Lys	Lys	Met	Tyr	Met	Glu
			180					185			.*		190		•
Phe	Pro	G1n	Leu	Tyr	Asn	Asn	Ser	Val	Val	Cys	Ser	Phe			Glu
		195				•	200					205	٠	•	
Va 1	Ha	Tvr	ive	Met	Aro	Gln	Thr	Asp	Arø	Asp	Va1	He	Thr	Ala	Leu

210	215		220
Thr His Arg Pro	Trp Ser Leu	Ser His Thr Gly	Asp Gly Lys Pro Arg
225	230	235	240
Tyr Asp Thr Phe	Trp Lys His	Phe Ile Phe Val	Met Met Asp Ile Leu
	245	250	255
Leu Asp Trp Ser	Met His Asn	Ile Leu Trp Tyr	Leu Cys Gly Ile Ser
260		265	270
Ala Phe Leu Met	Gln Lys Asp	Phe Val Ser Pro	Ala Tyr Leu Lys Lys
275	:	280	285
Trp Ser Ala Lys	Gly Ile Gln	Val Val Gly Trp	Thr Val Asn Thr Phe
290	295		300
Asp Glu Lys Ser	Tyr Tyr Glu	Ser His Leu Gly	Ser Ser Tyr Ile Thr
305	310	315	320
Asp Ser Met Val	Glu Asp Cys	Glu Pro His Phe	
	325	330	
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⟨211⟩ 345			
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Met Ser Pro Glu	Glu Trp Thr	Tyr Leu Val Val	Leu Leu Ile Ser Ile
1	5	10	15
Pro Ile Gly Phe	Leu Phe Lys	Lys Ala Gly Pro	Gly Leu Lys Arg Trp
, <b>20</b>		25	

Gly Ala Ala Ala V	al Gly Leu Gly I	Leu Thr Leu Ph	e Thr Cys G	ly Pro
35	40		45	
His Thr Leu His S	er Leu Val Thr	Ile Leu Gly Th	r Trp Ala L	eu Ile
	55		60	
50 Gln Ala Gln Pro (		Ala Leu Ala Lo	eu Ala Trp 1	Thr Phe
Gln Ala Gln Pro		75		80
<b>6</b> 5	10			Pro Thr
Ser Tyr Leu Leu	Phe Phe Arg Ala			95
	85	90		
Pro Thr Pro Phe	Thr Asn Ala Val	Gln Leu Leu I		Lys Leu
100		105	110	
Val Ser Leu Ala	Ser Glu Val Glm	Asp Leu His	Leu Ala Gln	Arg Lys
115	120	)	125	
Glu Met Ala Ser	Gly Phe Ser Lys	s Gly Pro Thr	Leu Gly Leu	Leu Pro
130	135	- V	140	
	Leu Met Glu Th	r Leu Ser Tyr	Ser Tyr Cys	Tyr Val
145	150	155		160
	r Gly Pro Phe Ph	ne Arg Tyr Arg	Thr Tyr Let	ı Asp Trp
Gly lie met in	165	170		175
a. a. D.	o Phe Pro Gly A		Leu Arg Pr	o Leu Leu
		185		0: :
18			ıleu Phe Le	eu Leu Ser
Arg Arg Ala Ti	rp Pro Ala Pro L	200 · ·	205	
195				
Ser His Leu P	he Pro Leu Glu A	Ala Val Arg Gl	u Asp Ala P	le tyr nia
210		•		
And Pro Tell P	ro Ala Arg Leu	Phe Tyr Met Il	e Pro Val P	he Phe Ala

SHENOVID JWO 0112660A2 1 3

225	<b>230</b> .	235	240
Phe Arg Met Arg Phe	Tyr Val Ala Trr	) Ile Ala Ala Gl	u Cys Gly Cys
245		250	255
Ile Ala Ala Gly Phe	Gly Ala Tyr Pro	Val Ala Ala Ly	s Ala Arg Ala
260	265		270
Gly Gly Gly Pro Thr	Leu Gln Cys Pro	Pro Pro Ser Ser	r Pro Glu Lys
275	280	285	
Ala Ala Ser Leu Glu	Tyr Asp Tyr Glu	Thr Ile Arg Asn	Ile Asp Cys
290	295	300	•
Tyr Ser Thr Asp Phe	Cys Val Arg Val	Arg Asp Gly Met	Arg Tyr Trp
005	310	315	320
Asn Met Thr Val Gln	Trp Trp Leu Ala	Gln Tyr Ile Tyr	
325		330	335
Pro Ala Arg Ser Tyr V	al Leu Arg Leu	•	
340	345		
⟨210⟩ 8	•	: *	
<211≻ 89			
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Met Tyr Met Gln Asp Ty	r Trp Arg Thr T	rp Leu Lys Gly [	eu Arg Gly
1 5			
Phe Phe Phe Val Gly Va	1 Leu Phe Ser A	la Val Ser Ile A	la Ala Phe
· · · · · · · · · 20			

Cys Thr Phe Leu Val Leu Ala Ile Thr Arg His Gln Ser Leu Thr Asp 35 40 Pro Thr Ser Tyr Tyr Leu Ser Ser Val Trp Ser Phe Ile Ser Phe Lys 60 50 👙 55 Trp Ala Phe Leu Leu Ser Leu Tyr Ala His Arg Tyr Arg Ala Asp Phe 75 65 70 Ala Asp Ile Ser Ile Leu Ser Asp Phe 85 <210> 9 <211> 406 <212> PRT <213> Homo sapiens <400> 9 Met Arg Gly Ser Val Glu Cys Thr Trp Gly Trp Gly His Cys Ala Pro 15 10 1 Ser Pro Leu Leu Leu Trp Thr Leu Leu Leu Phe Ala Ala Pro Phe Gly 30 20 25 Leu Leu Gly Glu Lys Thr Arg Gln Val Ser Leu Glu Val Ile Pro Asn 45 40 35 Trp Leu Gly Pro Leu Gln Asn Leu Leu His Ile Arg Ala Val Gly Thr 60 50 55 Asn Ser Thr Leu His Tyr Val Trp Ser Ser Leu Gly Pro Leu Ala Val 75 80 70 Val Met Val Ala Thr Asn Thr Pro His Ser Thr Leu Ser Val Asn Trp

	85			90	95	
Ser Leu Leu	Leu Ser	Pro Glu	Pro Asp	Gly Gly Le	eu Met Val Leu Pro	)
	100	•	105		110	
Lys Asp Ser	Ile Gln	Phe Ser	Ser Ala	Leu Val Ph	e Thr Arg Leu Leu	1
115			120		125	
Glu Phe Asp	Ser Thr	Asn Val	Ser Asp	Thr Ala Al	a Lys Pro Leu Gly	7
130	-	135		. 14		
Arg Pro Tyr	Pro Pro	Tyr Ser	Leu Ala	Asp Phe Se	r Trp Asn Asn Ile	)
145		150		155	160	)
Thr Asp Ser	Leu Asp	Pro Ala	Thr Leu	Ser Ala Th	r Phe Gln Gly His	>
	165			170	175	
Pro Met Asn	Asp Pro	Thr Arg	Thr Phe	Ala Asn Gl	y Ser Leu Ala Phe	<b>&gt;</b> •
	180		185		190	
Arg Val Gln	Ala Phe	Ser Arg	Ser Ser	Arg Pro Al	a Gln Pro Pro Arg	ζ
195			200		205	
Leu Leu His	Thr Ala	Asp Thr	Cys Gln	Leu Glu Va	l Ala Leu Ile Gly	7
210		215		. 22	0	
Ala Ser Pro	Arg Gly	Asn Arg	Ser Leu	Phe Gly Le	u Glu Val Ala Thr	<del>.</del>
225		230		235	240	)
Leu Gly Gln	Gly Pro	Asp Cys	Pro Ser	Met Gln Gl	u Gln His Ser Ile	<b>;</b>
	245			250	255	
Asp Asp Glu	Tyr Ala	Pro Ala	Val Phe	Gln Leu As	p Gln Leu Leu Trp	)
71 m	260	, · .,	., _ 265		270	
Gly Ser Leu	Pro Ser	Gly Phe	Ala Gln	Trp Arg Pr	o Val Ala Tyr Ser	•
275	45 % 4 %		280	ing and a second	285	

Gln Lys Pro	Gly	Gly	Arg	Glu	Ser	Ala	Leu	Pro	Cys	Gln	Ala	Ser	Pro
290		•	-	295	٠		•		300		•	•	
Leu His Pro	Åla	Leu	Ala	Tyr	Ser	Leu	Pro	Gln	Ser	Pro	Ile	Val	Arg
305			310	•			٠	315	•	**	•		320
Ala Phe Phe	Gly	Ser	Gln	Asn	Asn	Phe	Cys	Ala	Phe	Asn	Leu	Thr	Phe
• •		325			-		330	•			•	335	. •
Gly Ala Ser	Thr	Gly	Pro	Gly	Tyr	Trp	Asp	Gln	His	Tyr	Leu	Ser	Trp
	340					345					350		٠.
Ser Met Leu	Leu	G1y	Val	Gly	Phe	Pro	Pro	Val	Asp	Gly	Leu	Ser	Pro
355					360					365			
Leu Val Leu	Gly	Ile	Met	Ala	Val	Ala	Leu	Gly	Ala	Pro	Gly	Leu	Met
370				375					380			•	. *
Leu Leu Gly	Gly	Gly	Leu	Val	Leu	Leu	Leu	His	His	Lys	Lys	Tyr	Ser
385			390					395	<b>.</b>				400
Glu Tyr Glr	ı Ser	Ile	Asn				•					:	
		405											
													i
<210> 10													·
<211> 192										•			
<212> PRT													
<213> Homo	sapi	iens											
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Met Thr Al	a Vai	l Gly	/ Val	G1:	n Ala	Ğ1r	n Arı	g Pro	o Lev	ı G13	Glr	ı Arg	g Gln
1	٠.		5 .				. 10	)				15	5· · ·
Pro Arg Ar	g Se:	r Phe	e Phe	e Glo	u Sei	r Pho	e Ile	e Ar	g Thi	r Lei	ı Ile	e Ile	• Thr

			20					25					30		
Cys	Val	Ala	Leu	Ala	Val	Val	Leu	Ser	Ser	Val	Ser	Ile	Cys	Asp	Gly
		35		<b>.</b>			40		_			45			
His	Trp	Leu	Leu	Ala	Glu	Asp	Arg	Leu	Phe	Gly	Leu	Trp	His	Phe	Cys
	50					55					60				
Thr	Thr	Thr	Asn	Gln	Ser	Val	Pro	Ile	Cys	Phe	Arg	Asp	Leu	Gly	G1n
65	;				70					75					80
Ala	His	Val	Pro	Gly	Leu	Ala	Val	Gly	Met	Gly	Leu	Val	Arg	Ser	Val
				85					90					95	
Gly	Ala	Leu	Ala	Val	Val	Ala	Ala	Ile	Phe	Gly	Leu	Glu	Phe	Leu	Met
			100					105					110	,	
Val	Ser	Gln	Leu	Cys	Glu	Asp	Lys	His	Ser	Gln	Cys	Lys	Trp	Val	Met
		115					120					125			•
Gly	Ser	Ile	Leu	Leu	Leu	Val	Ser	Phe	Val	Leu	Ser	Ser	Gly	Gly	Leu
	130					135					140				-
Leu	Gly	Phe	Val	Ile	Leu	Leu	Arg	Asn	Gln	Val	Thr	Leu	Ile	Gly	Phe
145					150					155					160
Thr	Leu	Met	Phe	Trp	Cys	Glu	Phe	Thr	Ala	Ser	Phe	Leu	Leu	Phe	Leu
				165					170					175	
Asn	Ala	Ile	Ser	Gly	Leu	His	Ile	Asn	Ser	Ile	Thr	His	Pro	Trp	Glu
			180					185					190		
<210	)> 11		••						,				•		·
<211	> 80	)1					•				,		* .		
<212	> DN	IA								. ,	. غ ـ •				

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\ /. I .)/	LIUIUV	sapiens

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•	л	п	11	- >	•	1 1	

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gtgaeggtge aggageeegg eegeggegee eegeteaegt ttegeatega eegeggege 180

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ccagtta	cca	tgactcatcc	aggcactgga	gatattattg	ctgtcatgat	aacagaattg	480
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Gly       Met       Val         gtg       ttc       gcc       tct       gtc       tac       atc       tac       aga       tac         gtg       ttc       gcc       tct       gtc       ttc       tcc       atg       gg       gg</th><th>gag       gag       ccc       cca       caa       cat       cga       tcc       aag       agg         Glu       Glu       Glu       Pro       Pro       Glu       His       Arg       Ser       Lys       Arg         45       60       65       62       62       61       62       61</th><th>gag gag cag ccc cca caa cat cga tcc aag agg ggg         Glu Glu Gln Pro Pro Gln His Arg Ser Lys Arg Gly         45       50         ggc gtg tgc tac ctg tcg atg ggc atg gtc gtg ctg         Gly Val Cys Tyr Leu Ser Met Gly Met Val Val Leu         60       65         gtg ttc gcc tct gtc tac atc tac aga tac ttc ttt         Val Phe Ala Ser Val Tyr Ile Tyr Arg Tyr Phe Phe         75       80         gcc cga gat aac ttc ttc cgc tgt ggt gtg ctg tat         Ala Arg Asp Asn Phe Phe Arg Cys Gly Val Leu Tyr         90       95         100         tcc tcc cag gtc cgg act cag atg agg ctg gag agg         Ser Ser Gln Val Arg Thr Gln Met Glu Leu Glu Glu         105       110         110       115         tac ctc gac gag aac tac gag cgc atc aac gtg cct         Tyr Leu Asp Glu Asn Tyr Glu Arg Ile Asn Val Pro         125       130         ggc ggc ggt ggt gac cct gca gac atc atc cat gac ttc         Gly Gly Gly Asp Pro Ala Asp Ile Ile His Asp Phe         140       145         act gcg tac cat gat atc tcc ctg gac aag tgc tat         Thr Ala Tyr His Asp Ile Ser Leu Asp Lys Cys Tyr</th><th>gag gag cag ccc cca caa cat cga tcc aag agg agg agc         Glu Glu Gln Pro Pro Gln His Arg Ser Lys Arg Gly Ser         45         50           ggc gtg tgc tac ctg tcg atg ggc atg gtc gtg ctg ctc         Gly Val Cys Tyr Leu Ser Met Gly Met Val Val Leu Leu 60         65           gtg ttc gcc tct gtc tac atc tac aga tac ttc ttt ctt         Val Phe Ala Ser Val Tyr Ile Tyr Arg Tyr Phe Phe Leu 75         80         85           gcc cga gat aac ttc ttc cgc tgt ggt gtg ctg tat gag Ala Arg Asp Asn Phe Phe Arg Cys Gly Val Leu Tyr Glu 90         95         100           tcc tcc cag gtc cgg act cag atg aga ctg gag gag gat Ser Gln Val Arg Thr Gln Met Glu Leu Glu Glu Asp 115         115           tac ctc gac gag aac tac gag cgc atc aac gtg cct gtg ggc ggc ggt gac cct gca gac atc atc atc cat gac tc cag Gly Gly Gly Asp Pro Ala Asp Ile Ile His Asp Phe Gln 140         145           act gcg tac cat gat atc tcc ctg gac aag tgc tat gtc tat gtc         110         145           act gcg tac cat gat atc tcc ctg gac aag tgc tat gtc         110         145</th><th>gag gag cag ccc         cca caa cat cga tcc aag agg ggg agc tca           Glu Glu Gln Pro         Pro Gln His Arg Ser Lys Arg Gly Ser Ser           45         50           ggc gtg tgc tac ctg tcg atg ggc atg gtc gtg ctg ctc atg         Gly Val Cys Tyr Leu Ser Met Gly Met Val Val Leu Leu Met           60         65         70           gtg ttc gcc tct gtc tac atc tac aga tac ttc ttt ctt gca         Val Phe Ala Ser Val Tyr Ile Tyr Arg Tyr Phe Phe Leu Ala         Ass           75         80         85           gcc cga gat aac ttc ttc cgc tgt ggt gtg ctg tat gag gac         Ala Arg Asp Asn Phe Phe Arg Cys Gly Val Leu Tyr Glu Asp           90         95         100           tcc tcc cag gtc cag act cag atg gag ctg gaa gag gat gtg         gag gag gat gtg           Ser Ser Gln Val Arg Thr Gln Met Glu Leu Glu Glu Asp Val         110           105         110         115           tac ctc gac gag aac tac gag cgc atc aac gtg cct gtg ccc         125           Tyr Leu Asp Glu Asn Tyr Glu Arg Ile Asn Val Pro Val Pro         125           130         125           ggc ggc ggt gac cct gca gac atc atc cat gac ttc cag cgg           Gly Gly Gly Asp Pro Ala Asp Ile Ile His Asp Phe Gln Arg           140         145           150           act gcg tac cat gat atc tcc ctg gac aag tgc tat gtc           140</th><th>gag gag cag cag cag cag cag cag cag cag</th></th></td<>	gag       cag       ccc       cca       caa       cat         Glu       Glu       Gln       Pro       Gln       His         45        45         ggc       gtg       tgc       tac       ctg       tcg       atg         Gly       Val       Cys       Tyr       Leu       Ser       Met         60       60       45       tac       atc         8tg       ttc       gcc       tct       gtc       tac       atc         8tg       ttc       gcc       tct       gtc       tac       atc         8cc       cga       gat       aac       ttc       ttc       cgc         Ala       Arg       Asn       Phe       Phe       Arg         90       95       95       45       45       110       110         tac       tcc       cag       gtc       cgg       act       cag         Ser       Gln       Val       Arg       Thr       Gln         105       110       110       110       110         tac       ctc       gag       aac       tac       gag	gag       gag       cag       ccc       cca       caa       cat       cga         Glu       Glu       Gln       Pro       Gln       His       Arg         45         ggc       gtg       tgc       tac       ctg       tcg       atg       ggc         Gly       Val       Cys       Tyr       Leu       Ser       Met       Gly         gtg       ttc       gcc       tct       gtc       tac       atc       tac         Yal       Phe       Ala       Ser       Val       Tyr       Ile       Tyr         gcc       cga       gat       aac       ttc       ttc       cgc       tgt         Ala       Arg       Asn       Phe       Phe       Arg       Cys         gcc       cga       gat       cga       act       cag       atg         tcc       tcc       cag       gct       cgg       act       cag       atg         ser       Gln       Val       Arg       Thr       Gln       Arg         tcc       gac       gag       gac       tac       gac       gac         <	gag       gag       cag       ccc       cca       caa       cat       cga       tcc         Glu       Glu       Glu       Pro       Pro       Glu       His       Arg       Ser         ggc       gtg       tgc       tac       ctg       tcg       atg       ggc       atg         ggc       gtg       tgc       tac       ctg       tcg       met       Gly       Met         ggg       gtg       tcc       tct       gtc       tac       atc       tac       aga         gtg       ttc       gcc       tct       gtc       tac       atc       tac       aga         gcc       cga       gat       aac       ttc       ttc       cgc       tgt       ggt         gcc       cga       gat       aac       ttc       tcc       cgc       tgt       ggt         dala       Arg       Asn       Phe       Phe       Arg       Cys       Gly         dala       Arg       Glu       Arg       Thr       Glu       Met       Glu         dala       ctc       gag       aac       tac       gag       cgc       atc <th>gag       gag       cag       ccc       cag       cat       cgg       tcc       aag         Glu       Glu       Glu       Pro       Pro       Glu       His       Arg       Ser       Lys         45       15       15       50         ggc       gtg       tgc       tac       ctg       tcg       atg       gtc       atg       gtc         Gly       Val       Cys       Tyr       Leu       Ser       Met       Gly       Met       Val         gtg       ttc       gcc       tct       gtc       tac       atc       tac       aga       tac         gtg       ttc       gcc       tct       gtc       ttc       tcc       atg       gg       gg</th> <th>gag       gag       ccc       cca       caa       cat       cga       tcc       aag       agg         Glu       Glu       Glu       Pro       Pro       Glu       His       Arg       Ser       Lys       Arg         45       60       65       62       62       61       62       61</th> <th>gag gag cag ccc cca caa cat cga tcc aag agg ggg         Glu Glu Gln Pro Pro Gln His Arg Ser Lys Arg Gly         45       50         ggc gtg tgc tac ctg tcg atg ggc atg gtc gtg ctg         Gly Val Cys Tyr Leu Ser Met Gly Met Val Val Leu         60       65         gtg ttc gcc tct gtc tac atc tac aga tac ttc ttt         Val Phe Ala Ser Val Tyr Ile Tyr Arg Tyr Phe Phe         75       80         gcc cga gat aac ttc ttc cgc tgt ggt gtg ctg tat         Ala Arg Asp Asn Phe Phe Arg Cys Gly Val Leu Tyr         90       95         100         tcc tcc cag gtc cgg act cag atg agg ctg gag agg         Ser Ser Gln Val Arg Thr Gln Met Glu Leu Glu Glu         105       110         110       115         tac ctc gac gag aac tac gag cgc atc aac gtg cct         Tyr Leu Asp Glu Asn Tyr Glu Arg Ile Asn Val Pro         125       130         ggc ggc ggt ggt gac cct gca gac atc atc cat gac ttc         Gly Gly Gly Asp Pro Ala Asp Ile Ile His Asp Phe         140       145         act gcg tac cat gat atc tcc ctg gac aag tgc tat         Thr Ala Tyr His Asp Ile Ser Leu Asp Lys Cys Tyr</th> <th>gag gag cag ccc cca caa cat cga tcc aag agg agg agc         Glu Glu Gln Pro Pro Gln His Arg Ser Lys Arg Gly Ser 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125           ggc ggc ggt gac cct gca gac atc atc cat gac ttc cag cgg           Gly Gly Gly Asp Pro Ala Asp Ile Ile His Asp Phe Gln Arg           140         145           150           act gcg tac cat gat atc tcc ctg gac aag tgc tat gtc           140</th> <th>gag gag cag cag cag cag cag cag cag cag</th>	gag       gag       cag       ccc       cag       cat       cgg       tcc       aag         Glu       Glu       Glu       Pro       Pro       Glu       His       Arg       Ser       Lys         45       15       15       50         ggc       gtg       tgc       tac       ctg       tcg       atg       gtc       atg       gtc         Gly       Val       Cys       Tyr       Leu       Ser       Met       Gly       Met       Val         gtg       ttc       gcc       tct       gtc       tac       atc       tac       aga       tac         gtg       ttc       gcc       tct       gtc       ttc       tcc       atg       gg       gg	gag       gag       ccc       cca       caa       cat       cga       tcc       aag       agg         Glu       Glu       Glu       Pro       Pro       Glu       His       Arg       Ser       Lys       Arg         45       60       65       62       62       61       62       61	gag gag cag ccc cca caa cat cga tcc aag agg ggg         Glu Glu Gln Pro Pro Gln His Arg Ser Lys Arg Gly         45       50         ggc gtg tgc tac ctg tcg atg ggc atg gtc gtg ctg         Gly Val Cys Tyr Leu Ser Met Gly Met Val Val Leu         60       65         gtg ttc gcc tct gtc tac atc tac aga tac ttc ttt         Val Phe Ala Ser Val Tyr Ile Tyr Arg Tyr Phe Phe         75       80         gcc cga gat aac ttc ttc cgc tgt ggt gtg ctg tat         Ala Arg Asp Asn Phe Phe Arg Cys Gly Val Leu Tyr         90       95         100         tcc tcc cag gtc cgg act cag atg agg ctg gag agg         Ser Ser Gln Val Arg Thr Gln Met Glu Leu Glu Glu         105       110         110       115         tac ctc gac gag aac tac gag cgc atc aac gtg cct         Tyr Leu Asp Glu Asn Tyr Glu Arg Ile Asn Val Pro         125       130         ggc ggc ggt ggt gac cct gca gac atc atc cat gac ttc         Gly Gly Gly Asp Pro Ala Asp Ile Ile His Asp Phe         140       145         act gcg tac cat gat atc tcc ctg gac aag tgc tat         Thr Ala Tyr His Asp Ile Ser Leu Asp Lys Cys Tyr	gag gag cag ccc cca caa cat cga tcc aag agg agg agc         Glu Glu Gln Pro Pro Gln His Arg Ser Lys Arg Gly Ser         45         50           ggc gtg tgc tac ctg tcg atg ggc atg gtc gtg ctg ctc         Gly Val Cys Tyr Leu Ser Met Gly Met Val Val Leu Leu 60         65           gtg ttc gcc tct gtc tac atc tac aga tac ttc ttt ctt         Val Phe Ala Ser Val Tyr Ile Tyr Arg Tyr Phe Phe Leu 75         80         85           gcc cga gat aac ttc ttc cgc tgt ggt gtg ctg tat gag Ala Arg Asp Asn Phe Phe Arg Cys Gly Val Leu Tyr Glu 90         95         100           tcc tcc cag gtc cgg act cag atg aga ctg gag gag gat Ser Gln Val Arg Thr Gln Met Glu Leu Glu Glu Asp 115         115           tac ctc gac gag aac 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ctc	aac	acc	acc	att	gtg	ctg	ccc	cct	cgc	aac	ttc	tgg	gag	ctc	ctc	639
Leu	Asn	Thr	Thr	Ile	Val	Leu	Pro.	Pro	Arg	Asn	Phe	Trp	Glu	Leu	Leu	
•	, ,	170		,		-	175					180	.•	* -	•	
atg	aac	gtg	aag	agg	ggg	acc	tac	ctg	ccg	cag	acg	tac	atc	atc	cag	687
Met	Asn	Val	Lys	Arg	Gly	Thr	Tyr	Leu	Pro	G1n	Thr	Tyr	Ile	Ile	Gln	
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gag	gag	atg	gtg	gtc	acg	gag	cat	gtc	agt	gac	aag	gag	gcc	ctg	ggg '	735
Glu	Glu	Met	Val	Val	Thr	Glu	His	Val	Ser	Asp	Lys	Glu	Ala	Leu	Gly	
200					205					210					215	
tcc	ttc	atc	tac	cac	ctg	tgc	aac	ggg	aaa	gac	acc	tac	cgg	ctc	cgg	783
Ser	Phe	Ile	Tyr	His	Leu	Cys	Asn	Gly	Lys	Asp	Thr	Tyr	Arg	Leu	Arg	
				220					225					230		
cgc	cgg	gca	acg	cgg	agg	cgg	atc	aac	aag	cgt	ggg	gcc	aag	aac	tgc	831
Arg	Arg	Ala	Thr	Arg	Arg	Arg	Ile	Asn	Lys	Arg	Gly	Ala	Lys	Asn	Cys	
			235					240					245			
aat	gcc	atc	cgc	cac	ttc	gag	aac	acc	ttc	gtg	gtg	gag	acg	ctc	atc	879
Asn	Ala	Ile	Arg	His	Phe	G1u	Asn	Thr	Phe	Val	Val	Glu	Thr	Leu	Ile	
		250					255					260				
tgc	ggg	gtg	gtg	tga	ggcc	ctc	ctcc	ccca	ga a	cccc	ctgc	c gt	gttc	ctc	· X ·	930
Cys	Gly	Val	Val													
	265	٠													••	
ttt	tctt	ctt	tccg	gctg	ct c	tctg	gccc	t cc	tcct	tccc	cct	gctt	agc	ttgt	actttg	990
gac	gcgt	ttc	tata	gagg	tg a	catg	tctc	t cc	attc	ctct	сса	accc	tgc	ccac	ctccct	1050
gta	ccag	agc	tgtg	atct	ct c	ggtg	gggg	g cc	catc	tctg	ctg	acct	ggg	tgtg	gcggag	1110
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Met Ser Cys Ala Gly Arg Ala Gly Pro Ala Arg Leu Ala Ala -	

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g 9	gcg	aac	gac	gca	cgg	gca	ccg	tgg	ctg	agc	tgc	acc	ctg	ctg	gcc	ctc
ì	Ala	Asn	Asp	Ala	Arg	Ala	Pro	Trp	Leu	Ser	Cys	Thr	Leu	Leu	Ala	Leu
)	30					25					20					15
: 14	ccc	gag	cag	gtg	acg	gtg	aac	atc	ctc	gcg	acg	tac	tac	gag	cag	agc
•	Pro	Glu	Gln	Val	Thr	Val	Asn	Ile	Leu	Ala	Thr	Tyr	Tyr	Glu	Gln	Ser
		45					40					35	•			
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	Leu	Pro	Ala	Leu	Val	Gln	Gly	Arg	Val	Glu	Ala	Lys	Pro	Ser	Asp	Leu
				75					70					65		
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•	Arg	Thr	G1n	Pro	Asp	Cys	Gly	Leu	His	Asp	Ala	Val	Gly	His	Leu	Pro
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33	agg	cag	ctg	ttg	gcc	att	tgg	cag	aaa	atc	aat	cct	cct	gtc	ttt	ttc
	Arg	Gln	Leu	Leu	Ala	Ile	Trp	Gln	Lys	Ile	Asn	Pro	Pro	Val	Phe	Phe
	110					105			•		100					95
38	aat,	cac	ttc	gct	gcc	cgg	tca	ata	aaa	gag	aaa	ttt	acg	tgc	aac	gga
	Asn	His	Phe	Ala	Ala	Arg	Ser	Ile	Lys	Glu	Lys	Phe	Thr	Cys	Asn	Gly
		125					120	, •				115	,	-	. 0.	
43	gtt	cca	gag	gag	aaa	tcc	aaa	aat	aat	tac	atc	gtc	gta	gct	gtt	gca
	Val	Pro	Glu	Glu	Lys	Ser	Lys	Asn	Asn	Tyr	Ile	Val	Val	Ala	Val	Ala
			140					135				-	130	1		

acc	atg	act	cat	cca	ggc	act	gga	gat	att	att	gct	gtc	atg	ata	aca	478
Thr	Met	Thr	His	Pro	Gly	Thr	Gly	Asp	Ile	Ile	Ala	Val	Met	Ile	Thr ·	
		145		÷.			150		-			155			•	
gaa	ttg	agg	ggt	aag	gat	att	ttg	agt	tat	ctg	gag	aaa	aac	atc	tct	526
Glu	Leu	Arg	Gly	Lys	Asp	Ile	Leu	Ser	Tyr	Leu	Glu	Lys	Asn	Ile	Ser-	
	160					165					170		•			
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Val	G1n	Met	Thr	Ile	Ala	Val	Gly	Thr	Arg	Met	Pro	Pro	Lys	Asn	Phe	
175					180					185					190	
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Ser	Arg	Gly	Ser	Leu	Val	Phe	Val	Ser	Ile	Ser	Phe	Ile	Val	Leu	Met	
				195	•				200	٠.				205	0.50	
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Ile	Ile	Ser	Ser	Ala	Trp	Leu	Ile	Phe	Tyr	Phe	Ile	Gln	Lys	Ile	Arg	
			210					215					220	-		
tac	aca	aat	gca	cgc	gac	agg	aac	cag	cgt	cgt	ctc	gga	gat	gca	gcc	718
Tyr	Thr	Asn	Åla	Arg	Asp	Arg	Asn	Gln	Arg	Arg	Leu	Gly	Asp	Ala	Ala	
		225					230					235		•		
aag	aaa	gcc	atc	agt	aaa	ttg	aca	acc	agg	aca	gta	aag	aag	ggt	gac ·	766
Lys	Lys	Ala	Ile	Ser	Lys	Leu	Thr	Thr	Arg	Thr	Val	Lys	Lys	Gly	Asp	
•	240					245	×.				250					
aag	gaa	act	gac	cca	gac	ttt	gat	cat	tgt	gca	gtc	tgc	ata	gag	agc	814
Lys	Glu	Thr	Asp	Pro	Asp	Phe	Asp	His	Cys	Ala	Val	Cys	Ile	Glu	Ser	
255	٠.	٠.		-	260					265	ι .		5. × .	.r i	270	
tat	aag	cag	aat	gat	gtc	gtc	cga	att	ctc	ccc	tgo	aag	cat	gtt	ttc	862

Tyr	Lys	Gln	Asn	Asp	Val	Val	Arg	Ile	Leu	Pro	Cys	Lys	His	Val	Phe	
	:			275				٠	280	٠.				285	·	
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His	Lys	Ser	Cys	Val	Asp	Pro	Trp	Leu	Ser	Glu	His	Cys	Thr	Cys	Pro	
-		-	290	-	•			295					300			
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Met	Cys	Lys	Leu	Asn	Ile	Leu	Lys	Ala	Leu	Gly	Ile	Val	Pro	Asn	Leu	
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Pro	Cys	Thr	Asp	Asn	Val	Ala	Phe	Asp	Met	Glu	Arg	Leu	Thr	Arg	Thr	
	320					325					330					
caa	gct	gtt	aac	cga	aga	tca	gcc	ctc	ggc	gac	ctc	gcc	ggc	gac	aac	1054
Gln	Ala	Val	Asn	Arg	Arg	Ser	Ala	Leu	Gly	Asp	Leu	Ala	Gly	Asp	Asn	
335					340					345					350	
tcc	ctt	ggc	ctt	gag	cca	ctt	cga	act	tcg	ggg	atc	tca	cct	ctt	cct	1102
Ser	Leu	Gly	Leu	Glu	Pro	Leu	Arg	Thr	Ser	Gly	Ile	Ser	Pro	Leu	Pro	
-		٠.		355		• •		۸.	360				-	365	-	
cag	gat	ggg	gag	ctc	act	ccg	aga	aca	gga	gaa	atc	вас	att	gca	gta	1150
Gln	Asp	Gly	Glu	Leu	Thr	Pro	Arg	Thr	Gly	Glu	Ile	Asn	Ile	Ala	Val	
•			370	•			, .	375		••••	• 0		380			
aca	aaa	gaa	tgg	ttt	att	att	gcc	agt	ttt	ggc	ctc	ctc	agt	gcc	ctc	1198
Thr	Lys	Glu	Trp	Phe	Ile	Ile	Ala	Ser	Phe	Gly	Leu	Leu	Ser	Ala	Leu	
٠.		385	. :	, -	•	• •	390				•	395	- 1	•		
aca	ctc	tgc	tac	atg	atc	atc	aga	gcc	aca	gct	agc	ttg	aat	gct	aat	1246
Thr	Leu	Cys	Tyr	Met	Ile	Ile	Arg	Ala	Thr	Ala	Ser	Leu	Asn	Ala	Asn	

ANGULU - MU - UTSEEURS 1

400	405	•	410	?	
gag gta gaa tgg ttt	tgaagaagaa a	aaacctgct t	tctgactga t	tttgcctt	1300
Glu Val Glu Trp Phe			e ·		
415	e •		• (4)		
gaaggaaaaa agaacctat	t tttgtgcatc	atttaccaat	catgccacac	aagcatttat	1360
ttttagtaca ttttatttt	t tcataaaatt	gctaatgcca	aagctttgta	ttaaaagaaa	1420
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·					
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gggtgcaaac cccgagcgt	c tacgctgcc	atg agg ggc	gcg aac gc	c tgg gcg	233
	• -	Met Arg Gly	Ala Asn Ala	a Trp Ala	
*	٠	1	5	e d'a	
cca ctc tgc ctg ctg	ctg gct gcc	gcc acc cag	ctc tcg cg	g cag cag	28
Pro Leu Cys Leu Leu	Leu Ala Ala	Ala Thr Gln	Leu Ser Ar	g Gln Gln	
10	15		20 :	10 m	

BNSOCCID AWO 011286042 I

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Ser	Pro	Glu	Arg	Pro	Val	Phe	Thr	Cys	Gly	Gly	Ile	Leu	Thr	Gly	Glu	
25		•			30				-,	35					40	
tct	gga	ttt	att	ggc	agt	gaa	ggt	ttt	cct	gga	gtg	tac	cct	cca	aat	377
Ser	Gly	Phe	Ile	Gly	Ser	Glu	Gly	Phe	Pro	Gly	Val	Tyr	Pro	Pro	Asn	
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Ser	Lys	Cys	Thr	Trp	Lys	Ile	Thr	Val	Pro	Glu	Gly	Lys	Val	Val	Val	
			60					65					70	١		
ctc	aat	ttc	cga	ttc	ata	gac	ctc	gag	agt	gac	aac	ctg	tgc	cgc	tat	473
Leu	Asn	Phe	Arg	Phe	Ile	Asp	Leu	Glu	Ser	Asp	Asn	Leu	Cys	Arg	Tyr	
		75					80					85	;			
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Asp	Phe	Val	Asp	Val	Tyr	Asn	Gly	His	Ala	Asn	Gly	Glr	Arg	g Ile	Gly	
	90					95					100	)				
cgc	ttc	tgt	ggc	act	ttc	cgg	cct	gga	gcc	ctt	gtg	tco	agt	t ggo	aac	569
Arg	Phe	Cys	Gly	Thr	Phe	Arg	Pro	Gly	Ala	Leu	Val	Sea	r Sei	r Gly	y Asn	
105		-	,		110	)				115	<b>j</b>				120	
aag	atg	ate	gte	g cag	g atg	att	tct	gat	gcc	aac	ace	a gc	t gg	c aa	t ggc	617
Lys	Met	: Met	: Val	Glr	n Met	: Ile	Ser	r Asp	Ala	Asr	1 Thi	r Ala	a Gl	y As	n Gly	
				. 125	5				130	). '				13	5	
ttc	at	g gc	at	g tto	c tco	c gct	gc	t gaa	a cca	a aa	c ga	a ag	a gg	g ga	t cag	665
Phe	Me1	t Ala	a Me	t Pho	e Sei	r Ala	a Ala	a Glu	ı Pro	Ası	n Gl	u Ar	g Gl	y As	p Gln	
••	<u>.</u>	r	14	0 - 7.		, .	- :	145	5				.15	0	· · ·	
tat	t tg	t :gg:	a gg	a ct	c ct	t ga	c ag	a cc	t tc	c gg	c tc	t, tt	t aa	a ac	c ccc	713

BRIGHTYPID- JWO 1110860A2 I -

Tyr	Cys	Gly	Gly	Leu	Leu	Asp	Arg	Pro	Ser	Gly	Ser	Phe	Lys	Thr	Pro	
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Asn	Trp	Pro	Asp	Arg	Asp	Tyr	Pro	Ala	Gly	Val	Thr	Cys	Val	Trp	His	
	170		• •	. 8	•	175		•			180		. •	. 1		
att	gta	gcc	cca	aag	aat	cag	ctt	ata	gaa	tta	aag	ttt	gag	aag	ttt	809
Ile	Val	Ala	Pro	Lys	Asn	Gln	Leu	Ile	Glu	Leu	Lys	Phe	Glu	Lys	Phe	
185	•	•			190		•			195				,	200	
gat	gtg	gag	cga	gat	aac	tac	tgc	cga	tat	gat	tat	gtg	gct	gtg	ttt	857
Asp	Val	Glu	Arg	Asp	Asn	Tyr	Cys	Arg	Tyr	Asp	Tyr	Val	Ala	Val	Phe	
				205					210					215		
aat	ggc	ggg	gaa	gtc	aac	gat	gct	aga	aga	att	gga	aag	tat	tgt	ggt	905
Asn	Gly	Gly	Glu	Val	Asn	Asp	Ala	Arg	Arg	Ile	Gly	Lys	Tyr	Cys	Gly	
		•	220			*	-	225					230		÷	
gat	agt	cca	cct	gcg	cca	att	gtg	tct	gag	aga	aat	gaa	ctt	ctt	att	953
Asp	Ser	Pro	Pro	Ala	Pro	Ile	Val	Ser	Glu	Arg	Asn	Glu	Leu	Leu	Ile	
	٠.	235					240		٠	.,		245	2	. ,		
cag	ttt	tta	tca	gac	tta	agt	tta	act	gca	gat	ggg	ttt	att	ggt	cac	1001
Gln	Phe	Leu	Ser	Asp	Leu	Ser	Leu	Thr	Ala	Asp	Gly	Phe	Ile	Gly	His	
	250			,		255		٠			260	. •	•		4 Long	
tac	ata	ttc	agg	cca	aaa	aaa	ctg	cct	aca	act	aca	gaa	cag	cct	gtc	1049
Tyŕ	Ile	Phe	Arg	Pro	Lys	Lys	Leu	Pro	Thr	Thr	Thr	Glu	Gln	Pro	Val	
265					270 <sup>-</sup>	٠.		•	-	275			•	;	280	
acc	acc	aca	ttc	cct	gta	acc	acg	ggt	tta	888	acc	acc'	gtg	gcc	ttg	1097
Thr	Thr	Thr	Phe	Pro	Val	Thr	Thr	Gly ·	Leu	Lys	Thr	Thr	Val	Alá	Leu	

. 285	;	290 2	95
tgt caa caa aag tgt	aga cgg acg ggg	act ctg gag ggc aat t	at tgt 1145
Cys Gln Gln Lys Cys	Arg Arg Thr Gly	Thr Leu Glu Gly Asn T	yr Cys
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Ser Ser Asp Phe Val	l Leu Ala Gly Thr	Val Ile Thr Thr Ile T	hr Arg
315	320	325	
gat ggg agt ttg cad	c gcc aca gtc tcg	atc atc aac atc tac a	aaa gag 1241
Asp Gly Ser Leu His	s Ala Thr Val Ser	Ile Ile Asn Ile Tyr I	ys Glu
330	335	340	
gga aat ttg gcg at	t cag cag gcg ggc	aag aac atg agt gcc a	agg ctg 1289
Gly Asn Leu Ala Il	e Gln Gln Ala Gly	Lys Asn Met Ser Ala A	Arg Leu
345	350	355	360
act gtc gtc tgc aa	g cag tgc cct ctc	ctc aga aga ggt cta a	aat tac 1337
Thr Val Val Cys Ly	s Gln Cys Pro Leu	Leu Arg Arg Gly Leu	Asn Tyr
36	5	370	375
att att atg ggc ca	a gta ggt gaa gat	ggg cga ggc aaa atc	atg cca 1385
Ile Ile Met Gly Gl	n Val Gly Glu Asp	o Gly Arg Gly Lys Ile	Met Pro
380	385	390	
		c aag aat cag aag ctc	
Asn Ser Phe Ile Me	et Met Phe Lys Th	r Lys Asn Gln Lys Leu	Leu Asp
: 395	400	405	
gcc tta aaa aat a	ag caa tgt taacag	tgaa ctgtgtccat ttaago	1480
Ala Leu Lys Asn L	ys Gln Cys	· . · · · · · · · · · · · · · · · · · ·	
, <b>410</b>	. 415 .		repen

tgtattetge cattgeettt gaaagateta tgttetetea gtagaaaaaa aaataettat	1540
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gtacacggag cagcggcccc ggccccgcca acgctgccgc cggg atg ctc cag	233
Met Leu Gln	
the second of th	
acc ttg tat gat tac ttc tgg tgg gaa cgt ctg tgg ctg cct gtg aac	281
Thr Leu Tyr Asp Tyr Phe Trp Trp Glu Arg Leu Trp Leu Pro Val Asn	

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ttg acc tgg	gcc gat	cta gaa	gac cga	gat gga cg	gt gtc tac	gcc aaa	329
Leu Thr Trp	Ala Asp	Leu Glu	Asp Arg	Asp Gly Ar	g Val Tyr	Ala Lys	
20		<b>25</b> .		30		<b>35</b>	
gcc tca gat	ctc tat	atc acg	ctg ccc	ctg gcc tt	g ctc ttc	ctc atc	377
Ala Ser Asp	Leu Tyr	Ile Thr	Leu Pro	Leu Ala Le	u Leu Phe	Leu Ile	
•	. 40			45		50	
gtt cga tac	ttc ttt	gag ctg	tac gtg	gct aca cc	a ctg gct	gcc ctc	425
Val Arg Tyr	Phe Phe	Glu Leu	Tyr Val	Ala Thr Pr	o Leu Ala	Ala Leu	
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ttg aac ata	aag gag	aaa act	cgg ctg	cgg gca cc	t ccc aac	gcc acc	473
Leu Asn Ile	Lys Glu	Lys Thr	Arg Leu	Arg Ala Pro	o Pro Asn	Ala Thr	
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Leu Glu His	Phe Tyr	Leu Thr	Ser Gly	Lys Gln Pro	o Lys Gln	Val Glu	
85		90		9	<b>5</b> .	· .	
gta gag ctt	ttg tcc	cgg cag	agc ggg	ctc tct gg	c cgc cag	gta gag	569
Val Glu Leu	Leu Ser	Arg Gln	Ser Gly	Leu Ser Gly	y Arg Gln	Val Glu	
100		105		110		115	
cgt tgg ttc	cgt cgc	cgc cgc	aac cag	gac cgg cco	c agt ctc	ctc aag	617
Arg Trp Phe	Arg Arg	Arg Arg	Asn Gln	Asp Arg Pro	o Ser Leu	Leu Lys	
erit, e e	120			125	- «	130	
aag; ttc.cga	gaa gcc.	agc.tgg	aga ttc	aca ttt tad	c ctg att	gcc ttc	665
Lys Phe Arg	Glu Ala	Ser Trp	Arg Phe	Thr Phe Ty	r Leu Ile	Ala Phe	
3.13 11 5 y	135		. 140		145		

att	gcc	ggc	atg	gcc `	gtc	att	gtg	gat	aaa	ccc	tgg	ttc	tat	gac	atg	713
Ile	Ala	Gly	Met	Ala	Val	Ile	Val	Asp	Lys	Pro	Trp	Phe	Tyr	Asp	Met	
		150					155				•	160		•	.i	•
aag	aaa	gtt	tgg	gag	gga	tat	ccc	ata	cag	agc	act	atc	cct	tcc	cag -	761
Lys	Lys	Val	Trp	Glu	Gly	Tyr	Pro	Ile	Gln	Ser	Thr	Ile	Pro	Ser	Gln ·	
	165					170					175					
tat	tgg	tac	tac	atg	att	gaa	ctt	tcc	ttc	tac	tgg	tcc	ctg	ctc	ttc	809
Tyr	Trp	Tyr	Tyr	Met	Ile	G1u	Leu	Ser	Phe	Tyr	Trp	Ser	Leu	Leu	Phe	
180		•			185					190				(6)	195	
agc	att	gcc	tct	gat	gtc	aag	cga	aag	gat	ttc	aag	gaa	cag	atc	atc	857
Ser	Ile	Ala	Ser	Asp	Val	Lys	Arg	Lys	Asp	Phe	Lys	Glu	Gln	Ile	Ile	
				200					205	• 16				210	) '	•
cac	cat	gtg	gcc	acc	atc	att	ctc	atc	agc	ttt	tco	tgg	ttt	gco	aat	905
His	His	Val	Ala	Thr	Ile	Ile	Leu	Ile	Ser	Phe	Ser	Trp	Phe	Ala	Asn	
			215			•		220	)				225	*		
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Tyr	· Ile	· Arg	, Ala	Gly	Thr	Leu	Ile	Met	. Ala	Leu	ı His	s Asp	Ser	Sei	r Asp	
		230	)		•		235	;				240	)			
tac	cte	g cti	g gag	tca	a gcc	aag	ate	ttt	t aad	tac	c gc	g gga	a tgg	g aa	g aac	1001
Tyı	r Lei	ı Lei	ı Glu	ı Ser	r Ala	Lys	Met	: Phe	e Ası	n Ty	r Ala	a Gly	y Tr	p Ly	s Asn	
	24	5 '				250	<b>)</b>	•			25	5		÷		
ace	c tg	c aa	c aac	ato	c tto	ato	gto	tte	c gc	c at	t gt	t tt	t at	c at	c acc	1049
Th	г Су	s As	n Ası	n Ile	e Pho	e Ile	va:	l Ph	e Al	a Il	e Va	1 Ph	e Il	e Il	e Thr	
26						5										
cg	a ct	g gt	c at	c ct	g cc	c tto	tg:	g at	c ct	g ca	t tg	c ac	c ct	g gt	g tac	1097

Arg	Leu	Val	Ile	Leu	Pro	Phe	Trp	Ile	Leu	His	Cys	Thr	Leu	Val	Tyr	
				280		. *			285					290		
cca	ctg	gag	ctc	·tat	cct	gcc	ttc	ttt	ggc	tat	tac	ttc	ttc	aat	tcc	1145
Pro	Leu	Glu	Leu	Tyr	Pro	Ala	Phe	Phe	Gly	Tyr	Tyr	Phe	Phe	Asn	Ser	
			295					300					305			
atg	atg	gga	gtt	cta	cag	ctg	ctg	cat	atc	ttc	tgg	gcc	tac	ctc	att	1193
Met	Met	Gly	Val	Leu	Gln	Leu	Leu	His	Ile	Phe	Trp	Ala	Tyr	Leu	Ile	
		310					315					320			•	
ttg	cgc	atg	gcc	cac	aag	ttc	ata	act	gga	aag	ctg	gta	gaa	gat	gaa	1241
Leu	Arg	Met	Ala	His	Lys	Phe	Ile	Thr	Gly	Lys	Leu	Val	Glu	Asp	Glu	
	325					330					335					
cgc	agt	gac	cgg	gaa	gaa	aca	gag	agc	tca	gag	ggg	gag	gag	gct	gca -	1289
Arg	Ser	Asp	Arg	Glu	Glu	Thr	Glu	Ser	Ser	Glu	Gly	Glu	G1u	Ala	Ala	
340					345					350					355	
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Ala	Gly	Gly	Gly	Ala	Lys	Ser	Arg	Pro	Leu	Ala	Asn	Gly	His	Pro	Ile	
				360					365					370		
ctc	aat	aac	aac	cat	cgt	aag	aat	gac	tgaa	ccat	ta t	tcca	gctg	gc ct	ссса	1390
Leu	Asn	Asn	Asn	His	Arg	Lys	Asn	Asp		ė						-
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gatt	aatg	ca t	aaag	ccaa	g ga	acta	ccct	gct	ccct	gcg	ctat	aggg	tc a	cttt	aagct	1450
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⟨211⟩ 1973

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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agcgtcgcc atg gtc tgc agg gag cag tta tca aag aat cag gtc aag 168
Met Val Cys Arg Glu Gln Leu Ser Lys Asn Gln Val Lys

tgg gtg ttt gcc ggc att acc tgt gtg tct gtg gtg gtc att gcc gca 216

Trp	Val	Phe	Ala	Gly	Ile	Thr	Cys	Val	Ser	Val	Val	Val	Ile	Ala	Ala	
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Ile	Val	Leu	Ala	Ile	Thr	Leu	Arg	Arg	Pro	Gly	Cys	Glu	Leu	Glu	Ala	
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tgc	agc	cct	gat	gcc	gac	atg	ctg	gac	tac	ctg	ctg	agc	ctg	ggc	cag	312
Cys	Ser	Pro	Asp	Ala	Asp	Met	Leu	Asp	Tyr	Leu	Leu	Ser	Leu	Gly	Gln	
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atc	agc	cgg	cga	gat	gcc	ttg	gag	gtc	acc	tgg	tac	cac	gca	gcc	aac	360
Ile	Ser	Arg	Arg	Asp	Ala	Leu	Glu	Val	Thr	Trp	Tyr	His	Ala	Ala	Asn .	
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agc	aag	aaa	gcc	atg	aca	gct	gcc	ctg	aac	agc	aac	atc	aca	gtc	ctg	408
Ser	Lys	Lys	Ala	Met	Thr	Ala	Ala	Leu	Asn	Ser	Asn	Ile	Thr	Val	Leu	
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gag	gct	gac	gtc	aat	gta	gaa	ggg	ctc	ggc	aca	gcc	aat	gag	aca	gga	456
Glu	Ala	Asp	Val	Asn	Val	Glu	Gly	Leu	Gly	Thr	Ala	Asn	Glu	Thr	Gly	
: .	95	, .				100					105			•		•
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Val	Pro	Ile	Met	Ala	His	Pro	Pro	Thr	Ile	Tyr	Ser	Asp	Asn	Thr	Leu	
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Glu	Gln	Trp	Leu	Asp	Ala	Val	Leu	Gly	Ser	Ser	Gln	Lys	Gly	Ile	Lys	
•••			٠, ٠٠	130	. `				135					140	·	
ctg	gac	ttc	aag	aac	atc	aag	gca	gtg	ggc	ccc	tcc	ctg	gac	ctc	ctg .	600
Leu	Asp	Phe	Lys	Asn	Ile	Lys	Ala	Val	Gly	Pro	Ser	Leu	Asp	Leu	Leu	

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Arg	Gln	Leu	Thr	Glu	Glu	Gly	Lys	Val	Arg	Arg	Pro	Ile	Trp	Ile	Asn		
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gct	gac	atc	tta	aag	ggc	ccc	aac	atg	ctc	atc	tca	act	gag	gtc	aat		696
Ala	Asp	Ile	Leu	Lys	Gly	Pro	Asn	Met	Leu	Ile	Ser	Thr	Glu	Val	Asn		
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gcc	aca	cag	ttc	ctg	gcc	ctg	gtc	cag	gag	aag	tat	ccc	aag	gct	acc		744
Ala	Thr	Gln	Phe	Leu	Ala	Leu	Val	Gln	Glu	Lys	Tyr	Pro	Lys	Ala	Thr		
190					195					200				-	205		
cta	tct	cca	ggc	tgg	acc	acc	ttc	tac	atg	tcc	acg	tcc	cca	aac	agg		792
Leu	Ser	Pro	Gly	Trp	Thr	Thr	Phe	Tyr	Met	Ser	Thr	Ser	Pro	Asn	Arg		
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Thr	Tyr	Thr	Gln	Ala	Met	Val	G1u	Lys	Met	His	Glu	Leu	Val	Gly	Gly	•	•
		٠.,	225					230					235				
gtg	ccc	cag	agg	gtc	acc	ttc	cct	gta	cgg	tct	tcc	atg	gtg	cgg	gct		888
Val	Pro	Gln	Arg	Val	Thr	Phe	Pro	Val	Arg	Ser	Ser	Met	Val	Arg	Ala		
		240				•	245	٠				250			* *		
gcc	tgg	ccc	cac	ttc	agc	tgg	ctg	ctg	agc	caa	tct	gag	agg	tac	agc		936
Ala	Trp	Pro	His	Phe	Ser	Trp	Leu	Leu	Ser	Gln	Ser	Glu	Arg	Tyr	Ser		
	255					260					265			,	٠.		
ctg	acg	ctg	tgg	cag	gct	gcc	tcg	gac	ccc	atg	tcg	gtg	gaa	gat	ctg		984
															Leu		
		• :													285		

ctc	tac	gtc	cgg	gat	aac	act	gct	gtc	cac	caa	gtc	tac	tat	gac	atc	1032
Leu	Tyr	Val	Arg	Asp	Asn	Thr	Ala	Val	His	Gln <sub>.</sub>	Val	Tyr	Tyr	Asp	Ile	
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Phe	G1u	Pro	Leu	Leu	Ser	Gln	Phe	Lys	Gln	Leu	Ala	Leu	Asn	Ala	Thr	
			305					310					315			
cgg	aaa	cca	atg	tac	tac	aca	gga	ggc	agc	ctg	atc	cct	ctt	ctc	cag	1128
Arg	Lys	Pro	Met	Tyr	Tyr	Thr	Gly	Gly	Ser	Leu	Ile	Pro	Leu	Leu	Gln	
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ctg	cct	ggg	gat	gac	ggt	ctg	aat	gtg	gag	tgg	ctg	gtt	cct	gac	gtc	1176
Leu	Pro	Gly	Asp	Asp	Gly	Leu	Asn	Val	Glu	Trp	Leu	Val	Pro	Asp	Val	
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cag	ggc	agc	ggt	aaa	aca	gca	aca	atg	acc	ctc	cca	gac	aca	gaa	ggc	1224
Gln	Gly	Ser	Gly	Lys	Thr	Ala	Thr	Met	Thr	Leu	Pro	Asp	Thr	Glu	Gly	
350					355					360					365	
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Met	Ile	. Lei	. Leu	Asn	Thr	Gly	Leu	Glu	Gly	Thr	Val	Ala	Gli		Pro	
-				370					375					380		
															g tcc.	1320
Val															ı Ser	
			. 385										39			
															t ttg	1368
Cys	s Le	u Gl											'	e Hi	s Leu	
£		40												-	• •	
caa	a at	a gc	g ga	gcc	c gc	a gc	c ct	c cg	g cc	a tc	c ct	g gc	c <sub>.</sub> tt	g ct	g gca	1416

BRICHACIO MO UTINECURO I -

Gln	Ile	Ala	Glu	Pro	Ala	Ala	Leu	Arg	Pro	Ser	Leu	Ala	Leu	Leu	Ala	
	415	•				420					425	• •		, •		
cgc	ctc	tcc	agc	ctt	ggc	ctc	ttg	cat	tgg	cct	gtg	tgg	gtt	ggg	gcc	1464
Arg	Leu	Ser	Ser	Leu	Gly	Leu	Ļeu	His	Trp	Pro	Val	Trp	Val	Gly	Ala	
430					435					440		9 •		<b>- •</b> ·	~445	
aaa	atc	tcc	cac	ggg	agt	ttt	tcg	gtc	ccc	ggc	cat	gtg	gct	ggc	aga	1512
Lys	Ile	Ser	His	Gly	Ser	Phe	Ser	Val	Pro	Gly	His	Val	Ala	Gly	Arg	
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Glu	Leu	Leu	Thr	Ala	Val	Ala	Glu	Val	Phe	Pro	His	Val	Thr	Val	Ala	1
•	•		465				٠	470					475			
cca	ggc	tgg	cct	gag	gag	gtg	ctg	ggc	agt	ggc	tac	agg	gaa	cag	ctg	1608
Pro	Gly	Trp	Pro	Glu	Glu	Val	Leu	Gly	Ser	Gly	Tyr	Arg	Glu	Gln	Leu	
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ctc	aca	gat	atg	cta	gag	ttg	tgc	cag	ggg	ctc	tgg	caa	cct	gtg	tcc	1656
Leu	Thr	Asp	Met	Leu	Glu	Leu	Cys	Gln	Gly	Leu	Trp	Gln	Pro	Val	Ser	
•	495					500					505	•		,		
ttc	cag	atg	cag	gcc	atg	ctg	ctg	ggc	cac	agc	aca	gct	gga	gcc	ata	1704
Phe	Gln	Met	Gln	Ala	Met	Leu	Leu	Gly	His	Ser	Thr	Ala	Gly	Ala	<sup>:</sup> Ile	
510	٠	•	•		515	. ,		•		520			•		525	
ggc	agg	ctg	ctg	gca	tcc	tcc	ccc	cgg	gcc	acc	gtc	aca	gtg	gag	cac	1752
Gly	Arg	Leu	Leu	Ala	Ser	Ser	Pro	Arg	Ala	Thr	Val	Thr	Val	Glu	·His	
			•	530					535		. :		٠.	540	. 1	
aac	cca	gct	ggg	ggc	gac	tat	gcc	tct	gtg	agg	aca	gca	ttg	ctg	gca	1800
ÀSS	Dwa	410	G1 <sub>w</sub>	G1 <sub>v</sub>	Acn	Tur	Δ1a	Sar	Val	Ara	Thr	Ala	Lau	ررغ آ	· 41a	

545	<b>550</b>	555	
gct agg gct gtg gac agg a	acc cga gtc tac tac	agg cta ccc cag ggc	1848
Ala Arg Ala Val Asp Arg T	Thr Arg Val Tyr Tyr	Arg Leu Pro Gln Gly	
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tac cac aag gac ttg ctg g	gct cat gtt ggt aga	aac tgagcaccca ggggtg	1900
Tyr His Lys Asp Leu Leu A	Ala His Val Gly Arg	Asn	
575 5	580	585	
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gtgcgggcgc cggc atg tgg	ctg tgg gag gac cag	ggc ggc ctc ctg ggc	170
Met Trp	Leu Trp Glu Asp Gln	Gly Gly Leu Leu Gly.	
$p_{\mathbf{x}_{i}}$ , $q_{i}$ , $p_{i}$	5	10	
cct ttc tcc ttc ctg ctg	cta.gtg.ctg ctg ctg	gtg acg cgg agc ccg	218
Pro Phe Ser Phe Leu Leu	Leu Val Leu Leu Leu	Val Thr Arg Ser Pro	•

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gtc	aat	gcc	tgc	ctc	ctc	acc '	ggc	agc '	ctc	ttc	gtt	cta	ctg	cgc	gtc	266
Val	Asn	Ala	Cys	Leu	Leu	Thr	Gly	Ser	Leu	Phe	Val	Leu	Leu	Arg	Val	
	30					35			÷		40					
ttc	agc	ttt	gag	ccg	gtg	ссс	tct	tgc	agg	gcc	ctg	cag	gtg	ctc	aag ·	314
Phe	Ser	Phe	Glu	Pro	Val	Pro	Ser	Cys	Arg	Ala	Leu	Gln	Val	Leu	Lys	
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ccc	cgg	gac	cgc	att	tct	gcc	atc	gcc	cac	cgt	ggc	ggc	agc	cac	gac	362
Pro	Arg	Asp	Arg	Ile	Ser	Ala	Ile	Ala	His	Arg	Gly	Gly	Ser	His	Asp	
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Ala	Pro	Glu	Asn	Thr	Leu	Ala	Ala	Ile	Arg	Gln	Ala	Ala	Lys	Asn	Gly	
			80	)				85					90	)		;
gca	aca	ggc	gtg	gag	ttg	gac	att	gag	ttt	act	tct	gac	ggg	g ati	cct	458
Ala	Thr	· Gly	Val	Glu	Leu	Asp	Ile	Glu	Phe	Thr	Ser	. Ası	Gly	, I1e	e Pro	
		95	5				100	<b>)</b>				108	5			
gto	tta	ate	g cad	gat	; aac	aca	gta	gat	age	ace	act	t gai	t gg	g ac	t ggg	506
Va]	. Le	ı Met	t His	s Asp	Asn	Thr	· Val	. Ası	Are	g Thr	Th	r Asj	p G1;	y Th	r Gly	
	110	) ·				115	5.		•		12	0 -		•	٠ ; .	•
cġa	a tti	g tg	t ga	t ttį	g aca	tt1	t gaa	a caa	a ati	t ag	g aa	g ct	g aa	t cc	t gca	554
Ar	g Le	u Cy:	s As	p Lei	u Thi	r Phe	e Glu	ı Glı	n·Ile	e Ar	g Ly	s Le	u As	n·Pr	o Ala	
12	5		,	٠,	130	0	· •		- '	13	5	· •,			140	
gc	a aa	c ca	c ag	a ct	c ag	g aa	t ga	t tt	c cc	t ga	t ga	a aa	g at	c cc	t acc	602
															o Thr	
															55.	<u>:</u>

cta	agg	gaa	gct	gtt	gca	gag	tgc	cta	aac	cat	аас	ctc	aca	atc	ttc	650
Leu	Arg	Glu	Ala	Val	Ala	Glu	Cys	Leu	Asn	His	Asn	Leu	Lhi	Ile	Phe	-
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Phe	Asp	Val	Lys	Gly	His	Ala	His	Lys	Ala	Thr	Glu	Ala	Leu	Lys	Lys	
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	190					195					200					
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Phe	Leu	Pro	Glu	Val	Ile	Tyr	Lys	Met	Arg	Gln	Thr	Asp	Arg	Asp	Val	
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Gly	Lys	Pro	Arg	Tyr	Asp	Thr	Phe	Trp	Lys	His	Phe	Ile	Phe	Val	Met	
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Met	Asp	Ile	Leu	Leu	Asp	Trp	Ser	Met	His	Asn	Ile	Leu	Trp	Tyr	Leu	
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Cys	Gly	Ile	Ser	Ala	Phe	Leu	Met	Gln	Lys	Asp	Phe	Val	Ser	Pro	Ala	
	270					275					280			٠, ٠		
tac	tte	ลลฐ	ลลด	tee	tca	get.	ลลล	o o a	atc	cag	σtt	σtt	σσt	100	act	1034

Tyr Leu Lys Lys Trp Ser Ala Lys Gly Ile Gln Val Val Gly Trp Thr	
285 290 295 300	
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Val Asn Thr Phe Asp Glu Lys Ser Tyr Tyr Glu Ser His Leu Gly Ser	
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age tat ate act gae age atg gta gaa gae tge gaa eet cae tte	1127
Ser Tyr Ile Thr Asp Ser Met Val Glu Asp Cys Glu Pro His Phe	
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cagacc atg tcg cct gaa gaa tgg acg tat cta gtg gtt ctt ctt atc	288
Met Ser Pro Glu Glu Trp Thr Tyr Leu Val Val Leu Leu Ile	
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tcc atc ccc atc ggc ttc ctc ttt aag aaa gcc ggt cct ggg ctg aag	336
Ser Ile Pro Ile Gly Phe Leu Phe Lys Lys Ala Gly Pro Gly Leu Lys	
15 20 25 30	
aga tgg gga gca gcc gct gtg ggc ctg ggg ctc acc ctg ttc acc tgt	384
Arg Trp Gly Ala Ala Ala Val Gly Leu Gly Leu Thr Leu Phe Thr Cys	
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ggc ccc cac act ttg cat tct ctg gtc acc atc ctc ggg acc tgg gcc	432
Gly Pro His Thr Leu His Ser Leu Val Thr Ile Leu Gly Thr Trp Ala	
ctc att cag gcc cag ccc tgc tcc tgc cac gcc ctg gct ctg gcc tgg	480
Leu Ile Gln Ala Gln Pro Cys Ser Cys His Ala Leu Ala Leu Ala Trp	
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act ttc tcc tat ctc ctg ttc ttc cga gcc ctc agc ctc ctg ggc ctg	528
Thr Phe Ser Tyr Leu Leu Phe Phe Arg Ala Leu Ser Leu Leu Gly Leu	
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ccc act ccc acg ccc ttc acc aat gcc gtc cag ctg ctg ctg acg ctg	576
Pro Thr Pro Thr Pro Phe Thr Asn Ala Val Gln Leu Leu Thr Leu	

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Lys	Leu	Val	Ser	Leu	Ala	Ser	Glu	Val	Gln	Asp	Leu	His	Leu	Ala	Gln	
,		•		115				1	120					125		
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Arg	Lys	Glu	Met	Ala	Ser	Gly	Phe	Ser	Lys	Gly	Pro	Thr	Leu	Gly	Leu ·	
			130					135		• •		÷	140			
ctg	ссс	gac	gtg	ccc	tcc	ctg	atg	gag	aca	ctc	agc	tac	agc	tac	tgc	720
Leu	Pro	Asp	Val	Pro	Ser	Leu	Met	Glu	Thr	Leu	Ser	Tyr	Ser	Tyr	Cys	. •
		145					150					155				į
tac	gtg	gga	atc	atg	aca	ggc	ccg	ttc	ttc	cgc	tac	cgc	acc	tac	ctg	768
Tyr	Val	Gly	Ile	Met	Thr	Gly	Pro	Phe	Phe	Arg	Tyr	Arg	Thr	Tyr	Leu ·	
	160					165					170				. •	
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Asp	Trp	Leu	Glu	Gln	Pro	Phe	Pro	Gly	Ala	Val	Pro	Ser	Leu	Arg	Pro	
175	,				180					185	. •	* .			190	
ctg	ctg	cgc	cgc	gcc	tgg	ccg	gcc	ccg	ctc	ttc	ggc	ctg	ctg	ttc	ctg	864
Leu	Leu	Arg	Arg	Ala	Trp	Pro	Ala	Pro	Leu	Phe	Gly	Leu	Leu	Phe	Leu	
••		•		195					200	<u>.</u>				205	; <u>.</u>	
ctc	tcc	tct	cac	ctc	ttc	ccg	ctg	gag	gcc	gtg	cgc	gag	gac	gcc	ttc	912
Leu	Ser	Ser	His	Leu	Phe	Pro	Leu	Glu	Ala	Val	Arg	Glu	···Asp	Ala	Phe	
		-	210		٠.			215		•			220	): <b>t</b>		
tac	gcc	cgc	ccg	ctg	ccc	gcc	cgc	ctc	ttc	tac	atg	ato	ccc	gto	ttc	960
Tyr	Ala	Arg	Pro	Leu	Pro	Ala	Arg	Leu	Phe	Tyr	Met	Ile	Pro	Val	: Phe-	
<u>.</u> .		225				*	230	· .	· •		1 .	. 235	;. ·		P. 015	:

ttc gcc ttc cgc atg cgc	ttc tac gtg gcc t	gg att gcc gcc gag tgc 10	800
Phe Ala Phe Arg Met Arg	Phe Tyr Val Ala T	rp Ile Ala Ala Glu Cys	-
240	245	250	
ggc tgc att gcc gcc ggc	ttt ggg gcc tac c	cc gtg gcc gcc aaa gcc 10	056
Gly Cys Ile Ala Ala Gly	Phe Gly Ala Tyr P	ro Val Ala Ala Lys Ala	
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Tyr Trp Asn Met Thr Val	Gln Trp Trp Leu A	la Gln Tyr Ile Tyr Lys	
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Pr	o Pr	o Va	l As	p G1;	y Lei	ı Sei	r Pro	o Lei	u Va	l Le	u Gl	y Il	e Me	t Al	a Val	

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97 - 11 S S S S 24

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Gly	Pro	Thr	Asn	Ser	Thr	Thr	Arg	Pro	Pro	Ser	Thr	Pro	Glu	Gly	Ile		
			20					25					30				
Ala	Leu	Ala	Tyr	Gly	Ser	Leu	Leu	Leu	Met	Ala	Leu	Leu	Pro	Ile	Phe		
		35					40					45					
Phe	Gly	Ala	Leu	Arg	Ser	Val	Arg	Cys	Ala	Arg	Gly	Lys	Asn	Ala	Ser		
	50					55					60						
Asp	Met	Pro	Glu	Thr	Ile	Thr	Ser	Arg	Asp	Ala	Ala	Arg	Phe	Pro	Ile		
65		1			70					75					80		
Ile	Ala	Ser	Cys	Thr	Leu	Leu	Gly	Leu	Tyr	Leu	Phe	Phe	Lys	Ile	Phe		
	i v			85					90		-			95			
Ser	Gln	G1u	Tyr	Ile	Asn	Leu	Leu	Leu	Ser-	Met	Tyr	Phe	Phe	Val	Leu		
•	.; ,		100					105					110				
Gly:	Ile	Leu	Ala	Leu	Ser	His	Thr	Ile	Ser	Pro	Phe	Met	Asn	Lys	Phe :		

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		115					120					125		•.	٠.	-
Phe	Pro	Ala	Ser	Phe	Pro	Asn	Arg	Gln	Tyr	Gln	Leu	Leu	Phe	Thr	Gln	
	130					135	,				140		.,			
Gly	Ser	Gly	Glu	Asn	Lys	Glu	Glu	Ile	Ile	Asn	Tyr	Glu	Phe	Asp	Thr	
145					150					155					160	
Lys	Asp	Leu	Val	Cys	Leu	Gly	Leu	Ser	Ser	Ile	Val	Gly	Val	Trp	Tyr	
				165					170					175	٠.	
Leu	Leu	Arg	Lys	His	Trp	Ile	Ala	Asn	Asn	Leu	Phe	Gly	Leu	Ala	Phe	
			180					185					190			
Ser	Leu	Asn	Gly	Val	Glu	Leu	Leu	His	Leu	Asn	Asn	Val	Ser	Thr	Gly	
		195					200			•		205		,	•	
Cys	Ile	Leu	Leu	Gly	Gly	Leu	Phe	Ile	Tyr	Asp	Val	Phe	Trp	Val	Phe	;
	210					215					220					
Gly	Thr	Asn	Val	Met	Val	Thr	Val	Ala	Lys	Ser	Phe	Glu	Ala	Pro	Ile	<b>;</b>
225			,		230					235		•			240	)
Lys	Leu	Val	Phe	Pro	Gln	Asp	Leu	Leu	Glu	Lys	Gly	Leu	Glu	Ala	Asr	1
	;	; .		245					250	. ,	,	•		255	·	
Asn	Phe	Ala	Met	Leu	Gly	Leu	Gly	Asp	Val	Val	Ile	Pro	Gly	Ile	Phe	3
			260					265					270	, .		
Ile	Ala	Leu	Leu	Leu	Arg	Phe	Asp	Ile	Ser	Leu	Lys	Lys	s Asr	Thu	Hi	5
		275	5				280	)				285	5			•
Thr	- Tyr	r Phe	e Tyr	Thr	Ser	Phe	Ala	Ala	Tyr	· Ile	Phe	G1;	y Let	ı Gl	y Le	u
	290	) ·				295	5 .	. •,			300	). •	·: ·.		r. ***	٠:
Th	r Ile	e Phe	e Ile	e Met	t His	: Ile	e Phe	e Lys	His	s Ala	a Glr	ı Pro	o Ala	a Lei	u Le	u
309	5 ·: .	r (		<u>.</u>	· 310	)		"		319	5.	ı · -	٠.		- 32	0

Tyr	Leu	Val	Pro	Ala	Cys	Ile	Gly	Phe	Pro	Val	Leu	Val	Ala	Leu	Ala
				325					330					335	
Lys	Gly	Glu	Val	Thr	Glu	Met	Phe	Ser	Tyr	Glu	Glu	Ser	Asn	Pro	Lys
			340					345					350		
Asp	Pro	Ala	Ala	Val	Thr	Glu	Ser	Lys	Glu	Gly	Thr	Glu	Ala	Ser	Ala
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Ser	Lys	Gly	Leu	Glu	Lys	Lys	Glu	Lys							
	370		. 1			375									;
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<b>&lt;2</b> 11	1> 81	l													
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Met	Thr	Ala	His	Ser	Phe	Ala	Leu	Pro	Val	Ile	Ile	Phe	Thr	Thr	Phe
1			٠.	. <b>5</b>					10					15	٠.
Trp	G1y	Leu	Val	Gly	Ile	Ala	Gly	Pro	Trp	Phe	Val	Pro	Lys	Gly	Pro
	,		20					25					30		
Asn	Arg	Gly	Val	Ile	Ile	Thr	Met	Leu	Val	Ala	Thr	Ala	Val	Cys	Cys
	· . •	:. 35	• :				40					45			
Tyr	Leu	Phe	Trp	Leu	Ile	Ala	Ile	Leu	Ala	Gln	Leu	Asn	Pro	Leu	Phe
	.50	٠.	٠	٠.		55					60	•		÷	٠.٠
Gly	Pro	Gln	Leu	Lys	Asn	Glu	Thr	Ile	Trp	Tyr	Val	Arg	Phe	Leu	Trp
65	. د د د		, :		.70					, 75		· .			. 80
Glu									•	•				:	7

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		21.													
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<213	> Hc	omo s	apie	ns										٠.	
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Met	Gly	Asp	Thr	Gly	Leu	Arg	Lys	Arg	Arg	Glu	Asp	Glu	Lys	Ser	Ile
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Gln	Ser	Gln	Glu	Pro	Lys	Thr	Thr	Ser	Leu	Gln	Lys	Glu	Leu	Gly	Leu
			20					25					30		
Ile	Ser	Gly	Ile	Ser	Ile	Ile	Val	Gly	Thr	Ile	Ile	Gly	Ser	Gly	Ile ·
	ì	35					40					45 ·	٠.		
Phe	Val	Ser	Pro	Lys	Ser	Val	Leu	Ser	Asn	Thr	Glu	Ala	Val	Gly	Pro.
	50	•	٠,		-	55	. *				60				
Cys	Leu	Ile	Ile	Trp	Ala	Ala	Cys	Gly	Val	Leu	Ala	Thr	Leu	Gly	Ala
65	<u>.</u> •	. : •	:		70				٠.	.75	;				80
Leu	Cys	Phe	Ala	Glu	Leu	Gly	Thr	Met	Ile	Thr	Lys	Ser	Gly	Gly	Glu
				85					90	. •				-95	1 4
Tyr	Pro	Tyr	Leu	Met	Glu	Ala	Tyr	Gly	Pro	Ile	Pro	Ala	Tyr	Leu	Phe
		:	100	. •			٠,	105	,				110		• :
Ser	Trp	Ala	Ser	Leu	Ile	Val	Ile	Lys	Pro	Thr	Ser	Phe	Ala	Ile	Tle
:	11.	115	•	• •	. 1	. ·	120			٠,		125		•	••. •
															Cys
	120	1				125					140				+1

Lys	Pro	Pro	Gln	Ile	Val	Val	Lys	Cys	Leu	Ala	Ala	Ala	Ala	Ile	Leu
145					150					155					160
Phe	Ile	Ser	Thr	Val	Asn	Ser	Leu	Ser	Val	Arg	Leu	Gly	Ser	Tyr	Val
	: .	1		165					170					175	,
Gln	Asn	Ile	Phe	Thr	Ala	Ala	Lys	Leu	Val	Ile	Val	Ala	Ile	Ile	Ile
			180					185					190		
Ile	Ser	Gly	Leu	Val	Leu	Leu	Ala	Gln	Gly	Asn	Thr	Lys	Asn	Phe	Asp
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Asn	Ser	Phe	Glu	Gly	Ala	Gln	Leu	Ser	Val	Gly	Ala	Ile	Ser	Leu	Ala
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Phe	Tyr	Asn	Gly	Leu	Trp	Ala	Tyr	Asp	Gly	Trp	Asn	Gln	Leu	Asn	Tyr
225	٠.		٠		230					235					240
Ile	Thr	Glu	Glu	Leu	Arg	Asn	Pro	Tyr	Arg	Asn	Leu	Pro	Leu	Ala	Ile
				245					250					255	
Ile	Ile	Gly	Ile	Pro	Leu	Val	Thr	Ala	Cys	Tyr	Ile	Leu	Met	Asn	Val
		•	260					265					270	:	
Ser	Tyr	Phe	Thr	Val	Met	Thr	Ala	Thr	Glu	Leu	Leu	Gln	Ser	Gln	Ala
		275					280					285			
Val	Ala	Val	Thr	Phe	Gly	Asp	Arg	Val	Leu	Tyr	Pro	Ala	Ser	Trp	Ile
	290					295					300				
Val	Pro	Leu	Phe	Val	Ala	Phe	Ser	Thr	Ile	Gly	Ala	Ala	Asn	Gly	Thr
305					310					315				٠.	320
Cys	Phe	Thr	Ala	Gly	Arg	Leu	Ile	Tyr	Val	Ala	Gly	Arg	Glu	Gly	His
				325					330				•	335	
Met	Leu	Lys	Val	Leu	Ser	Tyr	Ile	Ser	Val	Arg	Arg	Leu	Thr	Pro	Ala

	340					345					350		
Pro Ala Ile	Ile	Phe	Tyr	Gly	Ile	Ile	Ala	Thr	Ile	Tyr	Ile	Ile	Pro
355				•	360	.•				365	•		
Gly Asp Ile	Asn	Ser	Leu	Val	Asn	Tyr	Phe	Ser	Phe	Ala	Ala	Trp	Leu
370		•		375			. •		380		,		
Phe Tyr Gly	Leu	Thr	Ile	Leu	G1y	Leu	Ile	Val	Met	Arg	Phe	Thr	Arg
385			390					395	. 0	•		• • •	400
Lys Glu Leu	Glu	Arg	Pro	Ile	Lys	Val	Pro	Val	Val	Ile	Pro	Val	Leu
	a <sup>a</sup>	405					410					415	• •
Met Thr Leu	Ile	Ser	Val	Phe	Leu	Val	Leu	Ala	Pro	Ile	Ile	Ser	Lys
	420					425					430		**
Pro Thr Trp	Glu	Tyr	Leu	Tyr	Cys	Val	Leu	Phe	Ile	Leu	Ser	Gly	Leu
435					440					445			, ·
Leu Phe Tyr	Phe	Leu	Phe	Val	His	Tyr	Lys	Phe	Gly	Trp	Ala	Gln	Lys
<b>450</b> ·		•	• •	455	• •				460				
Ile Ser Lys	Pro	Ile	Thr	Met	His	Leu	Gln	Met	Leu	Met	Glu	Val	Val
465		:	470		• 0	• •		475		:	•• 9		480
Pro Pro Glu	ı Glu	Asp	Pro	Glu									
		485	-	T		٠.	• •			•			5 ( 2 )
<210> 34		٠	٠		•	٠.	<b>.</b>		•	• (0 •	٠	•	
<211> 375													
<212> PRT	٠							· • ·	٠	• . • .			الانتها ويمو
<213≻ Ношо	sap	iens											
<400> 34·		• 10		٠٠ ،	. r .	. ' • 0	i • .	• 1		:		· /.	

Met	Thr	Pro	Gln	Pro	Ala	Gly	Pro	Pro	Asp	Gly	Gly	Trp	Gly	Trp	Val
.1	' <i>‡</i> .			5					. 10			• =		15	
Val	Ala	Ala	Ala	Ala	Phe	Ala	Ile	Asn	Gly	Leu	Ser	Tyr	Gly	Leu	Leu
•		.••	20		٠.			25		•			30	• 0	
Arg	Ser	Leu	Gly	Leu	Ala	Phe	Pro	Asp	Leu	Ala	Glu	His	Phe	Asp	Arg
		. 35					40					45			
Ser	Ala	Gln	Asp	Thr	Ala	Trp	Ile	Ser	Ala	Leu	Ala	Leu	Ala	Val	Gln
	- 50					55		:			60				
Gln	Ala	Ala	Ser	Pro	Val	Gly	Ser	Ala	Leu	Ser	Thr	Arg	Trp	Gly	Ala
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Arg	Pro	Val	Val	Met	Val	Gly	Gly	Val	Leu	Ala	Ser	Leu	Gly	Phe	Val
				85					90					95	
Phe	Ser	Ala	Phe	Ala	Ser	Gly	Leu	Leu	His	Leu	Tyr	Leu	Gly	Leu	Gly
			100					105					110		
Leu	Leu	Ala	Gly	Phe	Gly	Trp	Ala	Leu	Val	Phe	Ala	Pro	Ala	Leu	Gly
	•	115				•	120					125			
Thr	Leu	Ser	Arg	Tyr	Phe	Ser	Arg	Arg	Arg	Val	Leu	Ala	Val	Gly	Leu
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Ala	Leu	Thr	Gly	Asn	Gly	Ala	Ser	Ser	Leu	Leu	Leu	Ala	Pro	Ala	Leu
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Gln	Leu	Leu	Leu	Asp	Thr	Phe	Gly	Trp	Arg	Gly	Ala	Leu	Leu	Leu	Leu
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Gly	Ala	Ile	Thr	Leu	His	Leu	Thr	Pro	Cys	Gly	Ala	Leu	Leu	Leu	Pro
			180	٠				185					190		
Leu	Val	Leu	Pro	Gly	Asp	Pro	Pro	Ala	Pro	Pro	Arg	Ser	Pro	Leu	Ala

		195	•			•	200		•			205			
Ala	Leu	Gly	Leu	Ser	Leu	Phe	Thr	Arg	Arg	Ala	Phe	Ser	Ile	Phe	Ala
	210		٠.			215		٠.		•	220	:	0.	· · .	
Leu	Gly	Thr	Ala	Leu	Val	Gly	Gly	Gly	Tyr	Phe	Val	Pro	Tyr	Val	His
225		• :			230					235		:		÷	240
Leu	Ala	Pro	Arg	Phe	Arg	Pro	Gly	Pro	Gly	Gly	Ile	Arg	Ser	Ser	Ala
				245					250			•		255	٠,
Gly	Gly	Gly	Arg	Gly	Cys	Asp	Gly	Gly	Cys	Gly	Arg	Pro	Ala	Gly	Leu
			260				٠	265					270		
Arg	Val	Ala	Gly	Arg	Pro	Arg	Leu	Gly	Ala	Pro	Pro	Ala	Ala	Ala	Gly
	•	275					280				•	285			
Arg	Ile	Arg	Gly	Ser	Asp	Trp	Ala	Gly	Ala	Val	Gly	Gly	G1y	Ala	Gly
	290		٠	•		295	·.				300		•		
Ala	Arg	Gly	Gly	Arg	Arg	Arg	Glu	Leu	Gly	Gly	Ser	Pro	Ala	Gly	Arg
305					310		•			315	•	•			320
Gly	Cys	Gly	Leu	Trp	Ala	Glu	Arg	Gly	Glu	Leu	Arg	Pro	Ala	Gly	Phe
٠.				325					330			•		335	. * • •
Arg	Cys	Thr	Pro	Arg	Ala	Gly	Gly	Arg	Arg	Arg	Cys	Gly	Ala	Gly	His
.•	:		340		•	•	•	345				•	350	•	٠.
Arg	Ala	Gly	Asp	Asp	Ala	Asp	Glu	Pro	Arg	Gly	Ala	Pro	Gly	Pro	Ser
	·	355		. <i>*</i>	•	:	360		•	•		365			: .:·
Pro	Val	Arg	Leu	Pro	Lys	Gly						:			•
, ,.	370	.•	•			375	0.4	•		:	: .,	*	. 8	7.4	
													•		
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<212	>. PR	T													
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Pro	Glu	Trp	Gly	Gly	Phe	Glu	Glu	Asn	Ile	Gln	Gly	Gly	Gly	Ser	Ala
			20			•		25			•		30		
Val	Ile	Asp	Met	Glu	Asn	Met	Asp	Asp	Thr	Ser	Gly	Ser	Ser	Phe	Glu
		35					40					45			
Asp	Met	Gly	Glu	Leu	His	Gln	Arg	Leu	Arg	Glu	Glu	Glu	Val	Asp	Ala
	50					55					60				
Asp	Ala	Ala	Asp	Ala	Ala	Ala	Ala	Glu	Glu	Glu	Asp	Gly	Glu	Phe	Leu
65					70					75					80
Gly	Met	Lys	Gly	Phe	Lys	Gly	Gln	Leu	Ser	Arg	Gln	Val	Ala	Asp	Gln
		•		85					90		-			95	
Met	Trp	Gln	Ala	Gly	Lys	Arg	Gln	Ala	Ser	Arg	Ala	Phe	Ser	Leu	Tyr
			100					105					110		. •
Ala	Asn	Ile	Asp	Ile	Leu	Arg	Pro	Tyr	Phe	Asp	Val	Glu	Pro	Ala	Gln-
	.•	115	•	. •			120					125			
Val	Arg	Ser	Arg	Leu	Leu	Glu	Ser	Met	Ile	Pro	Ile	Lys	Met	Val	Asn
	130	)				135					140				· ;
Phe	Pro	Gln	Lys	Ile	Ala	Gly	Glu	Leu	Tyr	Gly	Pro	Leu	Met	Leu	Val
145	5				150	)				155					160
Phe	. Thr	Leu	ı Val	l Ala	lle	Leu	Leu	His	Gly	Met	Lys	Thr	Ser	. Asp	Thr:

			165					170					175	٠	:
Ile Ile	Arg	Glu	Gly	Thr	Leu	Met	Gly	Thr	Ala	Ile	Gly	Thr	Cys	Phe	
		180					185				٠.	190			:
Gly Tyr	Trp	Leu	Gly	Val	Ser	Ser	Phe	Ile	Tyr	Phe	Leu	Ala	Tyr	Leu	
	195	· ·				200	٠.				205		. *	6.7	
Cys Asn	Ala	Gln	Ile	Thr	Met	Leu	Gln	Met	Leu	Ala		Leu	G1v	Tvr	
210					215					220	,		٠.,		
	Pha	G1 v	Иic	Cvc		Vo1	Lou	Dha	Tla		Т	<b>4</b>	71.	11: _	
Gly Leu	ille	GIY			116	val	Leu	rne		ınr	ıyr	ASN	lle		
225				230					235					240	•
Leu His	Ala	Leu	Phe	Tyr	Leu	Phe	Trp	Leu	Leu	Val	Gly	Gly	Leu	Ser	
			245					250					255		
Thr Leu	Arg	Met	Val	Ala	Val	Leu	Val	Ser	Arg	Thr	Val	Gly	Pro	Thr	
٠		260		•			265					270			
Gln Arg	Leu	Leu	Leu	Cys	Gly	Thr	Leu	Ala	Ala	Leu	His	Met	Leu	Phe	
€.	275			٠.		280					285		: '		
Leu Leu	Tyr	Leu	His	Phe	Ala	Tyr	His	Lys	Val	Val-	Glu	Gly	Ile	Leu	
290			i.		295					300	,			· . ·	-
Asp Thr	Leu	G1 u	G1 v			Πe	Pro	Pro	٦١٥		Ara	Va 1	Pro	Ara	
305		,	01)			110		110		UIII	ur R				
	_			310	_				315	_				320	
Asp Ile															
•			325					330	•		٠. ٠		335		.*
Asn Ala															
1	.•	340	£			•	345			•	Ė	350	. · · · ·	*	•
٠.,				٠.٠	· .				•					ż	
<b>(210)</b> 36	ار خور	, .		. ,		٠, .	. ,			<i>:</i> ,	; ; ,		, 1 .,	,··	

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Commence of the second

<211	> 66	5 <b>7</b> :									,	. *			
<212	>, PF	RT <sub>.</sub>		<i>:</i> :		,. ·									
<213	) Ho	omo s	apie	ens									is .		
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Met	Ser	Ser	Gln	Pro	Ala	Gly	Asn	Gln	Thr	Ser	Pro	Gly	Ala	Thr	Glu
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Asp	Tyr	Ser	Tyr	Gly	Ser	Trp	Tyr	Ile	Asp	Glu	Pro	Gln	Gly	Gly	Glu
			20					25					30		
Glu	Leu	Gln	Pro	Glu	Gly	Glu	Val	Pro	Ser	Cys	His	Thr	Ser	Ile	Pro
		35					40					45			
Pro	Gly	Leu	Tyr	His	Ala	Cys	Leu	Ala	Ser	Leu	Ser	Ile	Leu	Val	Leu
	50	٠				55					60				
Leu	Leu	Leu	Ala	Met	Leu	Val	Arg	Arg	Arg	Gln	Leu	Trp	Pro	Asp	Cys
65					70					75					80
Val	Arg	Gly	Arg	Pro	Gly	Leu	Pro	Ser	Pro	Val	Asp	Phe	Leu	Ala	Gly
	· 1 .		٠.	85					90					95	
Asp	Arg	Pro	Arg	Ala	Val	Pro	Ala	Ala	Väl	Phe	Met	Val	Leu	Leu	Ser
			100	į				105					110		
Ser	Leu	Cys	Leu	Leu	Leu	Pro	Asp	Glu	Asp	Ala	Leu	Pro	Phe	Leu	Thr
	•	115	;				120		,			125	٠.		
Leu	Ala	. Ser	Ala	Pro	Ser	Gln	Asp	Gly	Lys	Thr	Glu	Ala	Pro	Arg	Gly
	130	)	•		÷	135					140	)			
Ala	Tr	Lys	, Ile	e Leu	Gly	Leu	Phe	Туг	Туг	Ala	Ala	Leu	Туг	Tyr	Pro
149	5,				150					155	5	: '			160
Let	ı Ala	a Ala	a Cys	s Ala	1 Thr	Ala	Gly	/ His	s Thi	r Ala	a Ala	His	s Lei	ı Let	ı Gly

					165					170					175		•
;	Ser	Thr	Leu	Ser	Trp	Ala	His	Leu	Gly	Val	Gln	Val	Trp	Gln	Arg	Ala	
				180					185				2	190			
(	Glu	Cys	Pro	Gln	Val	Pro	Lys	Ile	Tyr	Lys	Tyr	Tyr	Ser	Leu	Leu	Ala	
			195					200	ï			*	205			٠.	
:	Ser	Leu	Pro	Leu	Leu	Leu	Gly	Leu	Gly	Phe	Leu	Ser	Leu	Trp	Tyr	Pro	
		210			٠		215					220				٠,	
,	Val	Gln	Leu	Val	Arg	Ser	Phe	Ser	Arg	Arg	Thr	Gly	Ala	Gly	Ser	Lys	
:	225					230	•				235	٠				240	
(	Gly	Leu	Gln	Ser	Ser	Tyr	Ser	Glu	Glu	Tyr	Leu	Arg	Asn	Leu	Leu	Cys	
		- '			245					250	•				255		
4	Arg	Lys	Lys	Leu	Gly	Ser	Ser	Tyr	His	Thr	Ser	Lys	His	Gly	Phe	Leu	
		· i		260					265					270			
:	Ser	Trp	Ala	Arg	Val	Cys	Leu	Arg	His	Cys	Ile	Tyr	Thr	Pro	Gln	Pro	
		. •	275					280					285	1			
•	Gly	Phe	His	Leu	Pro	Leu	Lys	Leu	Val	Leu	Ser	Ala	Thr	Leu	Thr	Gly	
		290					295					300	• )	٠.	• 8	: '	
•	Thr	Ala	Ile	Tyr	Gln	Val	Ala	Leu	Leu	Leu	Leu	Val	Gly	Val	Val	Pro	
:	305				, ,	310					315		•	•	• •	320	
•																Leu	
	7			:	325		•		•	330				. '	335	** 3	1
]											-					Val	
	. •		•	340	٠.	<i>.</i>		•	345				0	350	<b>∴</b>	: 1	
(																Ser :	
		۰ ۵	355				,	360					365		٠, .	11 75	

RNSDOCID: «WO 0112660A2 I

4 - 1 - 1 - 1 - 1 - 1

Ala	Leu	Val	Leu	Ser	Cys	Leu	Leu	Thr	Phe	Leu	Val	Leu	Met	Arg	Ser
	370			-		375					380		-		
Leu	Val	Thr	His	Arg	Thr	Asn	Leu	Arg	Ala	Leu	His	Arg	Gly	Ala	Ala
385					390					395					400
Leu	Asp	Leu	Ser	Pro	Leu	His	Arg	Ser	Pro	His	Pro	Ser	Arg	G1n	Ala
	·			405					410					415	
Ile	Phe	Cys	Trp	Met	Ser	Phe	Ser	Ala	Tyr	Gln	Thr	Ala	Phe	Ile	Cys
			420					425				•	430		· -
Leu	Gly	Leu	Leu	Val	Gln	Gln	Ile	Ile	Phe	Phe	Leu	Gly	Thr	Thr	Ala
		435					440					445			
Leu	Ala	Phe	Leu	Val	Leu	Met	Pro	Val	Leu	His	Gly	Arg	Asn	Leu	Leu
	450					455					460				
Leu	Phe	Arg	Ser	Leu	Glu	Ser	Ser	Trp	Pro	Phe	Trp	Leu	Thr	Leu	Ala
465					470					475					480
Leu	Ala	Val	Ile	Leu	Gln	Asn	Met	Ala	Ala	His	Trp	Val	Phe	Leu	Glu
				485					490					495	÷ •
Thr	His	Asp	Gly	His	Pro	Gln	Leu	Thr	Asn	Arg	Arg	Val	Leu	Tyr	Ala
			500	)				505					510		
Ala	Thr	Phe	Leu	Leu	Phe	Pro	Leu	Asn	Val	Leu	Val	Gly	Ala	Met	Val
	. ,	.,515	5.	,			520	)		÷		525	5		
Ala	Thr	Tr	Arg	g Val	Leu	Leu	Ser	Ala	Leu	Tyr	Asr	ı Ala	Ile	His	Leu
	., <b>53</b> 0	) , .			• .	538	5		÷		-540	) .	. •		
G1 <sub>3</sub>	Glr	n Me	t, Asj	Lei	ı Sei	Let	ı Lev	Pro	Pro	Arg	g Ala	a Ala	Thr	Leu	ı Asp
548	5	. ·		. ; '	, 550	)				555	5	0			560
Pro	o Gly	y Ty:	r Ty	r Thi	r Tyi	r Arı	g Asr	n Phe	e Lei	ı Lys	s Ile	e Gl	u Val	l Sei	r Gln

		. !	565	• •				570			,		575	, ,
Ser His P	ro A	lal	Met	Thr	Ala	Phe	Cys	Ser	Leu	Leu	Leu	Gln	Ala	Gln
. 1 - 2	5	80 .					585	÷				590	:	
Ser Leu L	.eu P	ro A	Arg	Thr	Met	Ala	Ala	Pro	Gln	Asp	Ser	Leu	Arg	Pro .
5	95					600					605		.:	
Gly Glu G	lu A	.sp (	Glu	Gly	Met	Gln	Leu	Leu	Gln	Thr	Lys	Asp	Ser	Met
610			•		615					620	•			. , .
Ala Lys G	ly A	la A	Arg	Pro	Gly	Ala	Ser	Arg	Gly	Arg	Ala	Arg	Trp	Gly
625				630					635					640
Leu Ala T	yr T	hr l	Leu	Leu	His	Asn	Pro	Thr	Leu	Gln	Val	Phe	Arg	Lys
. *		(	645					650					655	
Thr Ala L	.eu L	.eu (	Gly	Ala	Asn	Gly	Ala	Gln	Pro					
•	. 6	60					665							
•														
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<211> 464	Į													
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<213> Hom	o sa	pie	ns											
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Met Ile V	al C	ys 1	Leu	Leu	Phe	Met	Met	Ile	Leu	Leu	Ala	Lys	Glu	Val
1.:		,	5		ı	:		:- 10			*.		15	· .
Gln Leu V	/al A	sp (	G1n	Thr	Asp	Ser	Pro	Leu	Leu	Ser	Leu	Leu	Gly	Gln
	•	20		· ·.	۰٠.		. 25	٠.		:	· •	30	• •	
Thr Ser S	Ser L	.eu :	Ser	Trp	His	Leu	Val	Asp	Ile	Val	Ser	Tyr	Gln	Ser
#11# .2%	35	; ;	1	••		40		٠.		, , , ,	45	:	. :	a si

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Lys	Glu	Ser	Tyr	Ala	Glu	Leu	Ile	Met	Lys	Leu	Leu	Lys	Val	Ser	Ala
65	٠.	1.			70					75		<b>.</b>			. 80
Gly	Leu	Ser	Ile	Pro	Thr	Asp	Ser	Gln	Lys	His	Leu	Asp	Ala	Val	Pro
				85					90					95	
Lys	Cys	Gln	Ala	Phe	Thr	His	Gln	Met	Val	Gln	Phe	Leu	Ser	Thr	Leu
			100					105					110		•••
Glu	Gln	Asn	Gly	Lys	Ile	Thr	Leu	Ala	Val	Leu	Glu	Gln	Glu	Met	Ser
		115					120					125			
Lys	Leu	Leu	Asp	Asp	Ile	Ile	Val	Phe	Asn	Pro	Pro	Asp	Met	Asp	Ser
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Gln	Thr	Arg	His	Met	Ala	Leu	Ser	Ser	Leu	Phe	Met	Glu	Val	Leu	Met
145			•		150					155					160
Met	Met	Asn	Asn	Ala	Thr	Ile	Pro	Thr	Ala	Glu	Phe	Leu	Arg	Gly	Ser
				165					170		,			175	٠ .
Ile	Arg	Thr	Trp	Ile	Gly	Gln	Lys	Met	His	Gly	Leu	Val	Val	Leu	Pro
			180					185					190		
Leu	. Leu	Thr	Ala	Ala	Cys	Gln	Ser	Leu	Ala	Ser	Val	Arg	His	Met	Ala
	· '	195	i ,,				200					205			ž.
Glu	Thr	Thr	Glu	Ala	Cys	Ile	Thr	Ala	Tyr	Phe	Lys	Glu	Ser	Pro	Leu
	210	) ,				215	;			: ·	220	)		.,	_ · · ·
Asn	Gln	Asr	Ser	Gly	Trp	Gly	Pro	Ile	Leu	Val	Ser	Leu	Gln	Val	Pro
225	<b>5</b> .				230	)				235	i				240
C1.		. Th.	- Mat	- 61.	. C1:	Phe	Len	Gir	Gli	ı Cvs	Lei	Thr	· Leu	ı G1 v	Ser

	245	. '	250		. •	255
Tyr Leu Thr	Leu Tyr	Val Tyr L	eu Leu Gln	Cys Leu	Asn Ser	Glu Gln
	260		265		270	•
Thr Leu Arg	Asn Glu	Met Lys V	al Leu Leu	Ile Leu	Ser Lys	Trp Leu
275		. 2	280		285	e Seat each
Glu Gln Val	Tyr Pro	Ser Ser \	/al Glu Glu	Glu Ala	Lys Leu	Phe Leu
290	•	295		300		-
Trp Trp His	Gln Val	Leu Gln l	Leu Ser Leu	Ile Gln	Thr Glu	Gln Asn
305		310		315		320
Asp Ser Val	Leu Thr	Glu Ser	Val Ile Arg	Ile Leu	Leu Leu	Val Gln
	325		330	•		335
Ser Arg Gla	n Asn Leu	Val Ala	Glu Glu Arg	Leu Ser	Ser Gly	Ile Leu
	340		345		350	I
Gly Ala Il	e Gly Phe	Gly Arg	Lys Ser Pro	Leu Ser	· Asn Arg	Phe Arg
35	5		360		365	e i.i. a
Val Val Al	a Arg Ser	Met Ala	Ala Phe Leu	ı Ser Val	Gln Val	Pro Met
370	· Y ,	375		380		,
Glu Asp Gl	n Ile Arg	g Leu Arg	Pro Gly Ser	r Glu Lei	ı His Lev	ı Thr Pro
385	i	390		395		400
Lys Ala Gl	n Gln Ala	a Leu Asn	Ala Leu Gl	u Ser Me	t Ala Se	r Ser Lys
	40	5 ·	: 41	0 .		415 -
Gln Tyr Va	al Glu Ty	r Gln Asp	Gln Ile Le	u Gln Al	a Thr Gl	n Phe Ile
	420	ì	425		· · 43	<b>0</b>
Arg His P	ro Gly Hi	s Cys Leu	Gln Asp Gl			
. 4	35		440		445	Section Const.

Leu	ı Val	. Asr	n Cys	s Lei	ı Tyr	Pro	Glu	ı Val	l His	s Ty	r Lei	ı Ası	o His	: Ile	Arg
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⟨21	3> H	omo	sapi	ens											
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Leu	Leu	Gly	Thr	Ala	Ala	Gly	Leu	G1y	Phe	Leu	Cys	Leu	Leu	Tyr	Ser
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Gln	Arg	Trp	Lys	Arg	Thr	Gln	Årg	His	Gly	Arg	Ser	Gln	Ser	Leu	Pro
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Asn	Ser	Leu	Asp	Tyr	Thr	Gln	Thr	Ser	Asp	Pro	Gly	Arg	His	Val	Met
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Leu	Leu	Arg	Ala	Val	Pro	Gly	Gly	Ala	Gly	Asp	Ala	Ser	Val	Leu	Pro
65					70					75					80
Ser	Leu	Pro	Arg	Glu	Gly	Gln	Glu	Lys	Val	Leu	Asp	Arg	Leu	Asp.	Phe
,	•, •	~ <i>t</i>		85			٠.		90		ı			95	
Val	Leu	Thr	Ser	Leu	Val	Ala	Leu	Arg	Arg	Glu	Val	Glu	Glu	Leu	Arg
٠٠.	. ~	•_	100			; <b>,</b>	•	105				,	110	,· · · .	٠,٠
													Val		
tr.	4 -	115					120				٠.	125			
His	Met	Glu	Glu	Asn	Gln	Aro	Va 1	412	Ara	A == ==	1	A 2	Dho	Dwa	Dha

	130	* =	£) '	* * .	, •	135					140	•. •		'	
Val	Arg	Glu	Arg	Ser	Asp	Ser	Thr	Gly	Ser	Ser	Ser	Val	Tyr	Phe	Thr
145		•			150					155					160
Ala	Ser	Ser	Gly	Ala	Thr	Phe	Thr	Asp	Ala	Glu	Ser	Glu	Gly	Gly	Tyr
				165					170					175	
Thr	Thr	Ala	Asn	Ala	Glu	Ser	Asp	Asn	Glu	Arg	Asp	Ser	Asp	Lys	Glu
			180					185				,	190		
Ser	Glu	Asp	Gly	Glu	Asp	Glu	Val	Ser	Cys	Glu	Thr	Val	Lys	Met	Gly
,		195					200					205			
Arg	Lys	Asp	Ser	Leu	Asp	Leu	Glu	Glu	Glu	Ala	Ala	Ser	Gly	Ala	Ser
	210	<b>;</b>				215					220			,	
Ser	Ala	Leu	Glu	Ala	Gly	Gly	Ser	Ser	Gly	Leu	Glu	Asp	Val	Leu	Pro
225	, i				230					235					240
Leu	Leu	Gln	Gln	Ala	Asp	Glu	Leu	His	Arg	Gly	Asp	Glu	Gln	Gly	Lys
		•		245	•				250			ŧ		255	
Arg	Glu	ı Gly	Phe	e Gln	Leu	Leu	Leu	Asn	Asn	Lys	Leu	Val	Tyr	Gly	Ser
			260	)		٠.		265	,				270	,	
Arg	g Glr	n Asp	Phe	e Lei	ı Trp	Are	Leu	ı Ala	Arg	Ala	Tyr	Ser	· Asp	Met	Cys
		279	5				280	)		٠.		285	;	-	
Gli	u Lei	u Thi	r Glu	u Glı	ı Val	l Sei	r Glu	ı Lys	Lys	Ser	Tyr	Ala	ı Leu	Asp	Gly
	: 29	0 -	• •			298	5		٠.		300			• •	
Ly	s Gl	u Gl	u Ala	a Gl	u Ala	a Ala	a Leu	ı Glu	ı Lys	s Gly	y Asp	Glu	ı Ser	· Ala	a Asp
30	5		•		. 31	0	•			315	5			*	320
Су	s Hi	s Le	u Tr	р Ту	r Al	a Va	l Le	u Cy:	s Gly	y Gli	n Lei	ı Ala	a Glu	ı Hi	s Glu
	ا.			32			1								5 :

Ser Ile Gln Arg Arg Ile Gln Ser Gly Phe Ser Phe Lys Gl	u His Val
340 345 35	50
Asp Lys Ala Ile Ala Leu Gln Pro Glu Asn Pro Met Ala Hi	s Phe Leu
355 360 . 365	
Leu Gly Arg Trp Cys Tyr Gln Val Ser His Leu Ser Trp Le	u Glu Lys
370 375 380	
Lys Thr Ala Thr Ala Leu Leu Glu Ser Pro Leu Ser Ala Th	r Val Glu
385 390 395	400
Asp Ala Leu Gln Ser Phe Leu Lys Ala Glu Glu Leu Gln Pr	o Gly Phe
405 410	415
Ser Lys Ala Gly Arg Val Tyr Ile Ser Lys Cys Tyr Arg Gl	u Leu Gly
420 425 43	0
Lys Asn Ser Glu Ala Arg Trp Trp Met Lys Leu Ala Leu Gl	u Leu Pro
435 440 445	
Asp Val Thr Lys Glu Asp Leu Ala Ile Gln Lys Asp Leu Gl	u Glu Leu
450 455 460	٠.
Glu Val Ile Leu Arg Asp	٠.
465 470	
⟨210⟩ 39	8 · · · ·
⟨211⟩ 243	
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Met Glu Gln Gly Ser Gly Arg Leu Glu Asp Phe Pro Val Ass	

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1				5					10		÷			15	
Ser	Val	Thr	Pro	Tyr	Thr	Pro	Ser	Thr	Ala	Asp	Ile	Gln	Val	Ser	Asp
	•		20					25					30	,	• :
Asp	Asp	Lys	Ala	Gly	Ala	Thr	Leu	Leu	Phe	Ser	Gly	Ile	Phe	Leu	G1y
		35					40					45		•	. 2
Leu	Val	Gly	Ile	Thr	Phe	Thr	Val	Met	Gly	Trp	Ile	Lys	Tyr	Gln	Gly
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Val	Ser	His	Phe	Glu	Trp	Thr	Gln	Leu	Leu	Gly	Pro	Val	Leu	Leu	Ser
65					70					75					80
		Val	Thr	Phe	Ile	Leu	Ile	Ala	Val	Cys	Lys	Phe	Lys	Met	Leu
				85					90					95	
Ser	- Cys	Glr	ı Lei	ı Cys	Lys	Glu	Ser	Glu	Glu	Arg	Val	Pro	Asp	Ser	Glu
			100					105		•			110		
Glr	ı Thi	r Pro	o G1;	, Gly	Pro	Ser	- Phe	. Val	Phe	e Thi	- Gly	ı Ile	Asr	Glr	n Pro
		11					120					125		, *	
Ile	e Thi	r Ph	e Hi:	s Gly	/ Ala	a Thi	r Val	l Val	Gli	n Tyi	r Il	e Pro	o Pro	o Pro	o Tyr
	130					13					14			, ,	,
Gl			o G1	u Pr	o Me	t Gl	y Il	e Ası	n Th	r Se	r Ty	r Le	u Gl	n Se	r Val
14					15					15					160
		r Pr	о Су	s Gl	y Le	u Il	e Th	r Se	r Gl	y Gl	y Al	a Al	a Al	a Al	a Met
			•	16					17						5
Se	er Se	r Pr	o Pr			r Ty	r Th	r Il	е Ту	r Pr	o Gl	n As	p As	n Se	r'Ala
		- ··	18		•	•		18							· . !''
pı	ne Va	al V2			u Gl	y Cv	rs Le			ne Th	ır As	sp Gl	ly G1	ly As	sn'His'
															1 . 1

Ar	g Pro	Ası	n Pro	As <sub>l</sub>	o Va	l Asp	Glr	Leu	Glu	ı Glu	ı Thi	r Gli	n Lei	u Gl	u Glu
	210	)				215	;				220	)			
Gl	ı Ala	. Cys	s Ala	Cys	s Phe	Ser	Pro	Pro	Pro	Tyr	Glu	ı Glu	ı Ile	e Ty	r Ser
22	5			•	230	)				235	i				240
Let	ı Pro	Arg	5												-
	•														
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Asp	Glu	Ala	Ser	Cys	Cys	Arg	Trp	Gly	Ala	Gln	His	Ala	Gly	Ala	Arg
	-		20					25					30		
Glu	Leu	Ala	Ala	Leu	Tyr	Ser	Pro	Gly	Lys	Arg	Leu	Gln	Glu	Trp	Cys
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Ser	Val	Ile	Leu	Cys	Phe	Ser	Leu	Ile	Ala	His	Asn	Leu	Val	His	Leu
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Val	Ala	Gly	Ala	Leu	Ile	Ala	Asp	Phe	Leu	Ser	Gly	Leu	Val	His	
				85					90		-			95	· •
Gly	Ala	Asp	Thr	Trp	Gly	Ser	Val	Glu		Pro	Ile	Val	Glv		Ala
													,	_,_	

BNGDYCID->WO OTTORROAD I >

Phe Ile Arg Pro Phe Arg Glu His His Ile Asp Pro Thr Ala Ile Thr	
115 120 125	
Arg His Asp Phe Ile Glu Thr Asn Gly Asp Asn Cys Leu Val Thr Leu	
130 135 140	
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145 150 155 160	
Ala Leu Glu Gln Leu Tyr Pro Trp Glu Cys Phe Val Phe Cys Leu Ile	
165 170 175	
lle Phe Gly Thr Phe Thr Asn Gln Ile His Lys Trp Ser His Thr Tyr	٠.
180 185 190	
Phe Gly Leu Pro Arg Trp Val Thr Leu Leu Gln Asp Trp His Val Ile	
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Leu Pro Arg Lys His His Arg Ile His His Val Ser Pro His Glu Thr	
210 215 220	
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225 230 235 240	<b>)</b>
Gly Phe Trp Arg Arg Leu Glu Asp Leu Ile Gln Gly Leu Thr Gly Glu	1
245 250 255	. '
Lys Pro Arg Ala Asp Asp Met Lys Trp Ala Gln Lys Ile Lys	
260 265 270	. *
	. 5.*
⟨210⟩ 41° · · · · · · · · · · · · · · · · · · ·	
⟨211⟩ 1131	
⟨212⟩ DNA	11.
<213> Homo sapiens	

<400> 41

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720

780

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Met Phe Ser Tyr Glu Glu Ser Asn Pro Lys Asp Pro Ala Ala Val Thr	
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Lys Glu Lys	
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Ile Trp Tyr Val Arg Phe Leu Trp Glu	
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Val	Gly	Pro	Cys	Leu	Ile	Ile	Trp	Ala	Ala	Cys	Gly	Val	Leu	Ala	Thr		
	× .		65					70					75		. •		
ctg	ggt	gcc	ctg	tgc	ttt	gcg	gag	ctt	ggc	aca	atg	atc	acc	aag	tca		468
Leu	Gly	Ala	Leu	Cys	Phe	Ala	Glu	Leu	Gly	Thr	Met	Ile	Thr	Lys	Ser		
		80					85					90			• .		
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Gly	Gly	Glu	Tyr	Pro	Tyr	Leu	Met	Glu	Ala	Tyr	Gly	Pro	Ile	Pro	Ala		
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Tyr	Leu	Phe	Ser	Trp	Ala	Ser	Leu	Ile	Val	Ile	Lys	Pro	Thr	Ser	Phe		
110	<b>.</b>	٠,			115		• •			120	• :	٠.	, •		125		
gcc	atc	atc	tgc	ctc	agc	ttc	tcc	gag	tat	gtg	tgt	gcg	ccc	ttc	tat.	6	512
Ala	Ile	Ile	Cys	Leu	Ser	Phe	Ser	Glu	Tyr	Val	Cys	Ala	Pro	Phe	Tyr		
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Val	Gly	Cys	Lys	Pro	Pro	Gln	Ile	Val	Val	Lys	Cys	Leu	Ala	Ala	Ala		
		٠.	145				٠.	150	٠.	- •		٠	155		·		
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Ala	Ile	Leu	Phe	Ile	Ser	Thr	Val	Asn	Ser	Leu	Ser	Val	Arg	Leu	Gly		47.
	-	160		ŕ			165					170					
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Ser	Tyr	Val	Gln	Asn	Ile	Phe	Thr	Ala	Ala	Lys	Leu	Val	Ile	Val	Ala.		
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Ile	Ile	Ile	Ile	Ser	Gly	Leu	Val	Leu	Leu	Ala	Gln	Gly	Asr	1 Tha	Lys		
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Asn	Phe	e Asp	Asr	ı Ser	Phe	Glı	Gly	Ala	Gln	Leu	Ser	· Val	Gl	y. Ala	a Ile	•	
		;		210	)				215			•	٠	220	<b>)</b> ; '	-	
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Sei	r::Lei	ı Ala	a Pho	e Ty	r Ası	n Gl	y Leu	Trp	Ala	Туз	. Ası	G1;	y Tr	p As	n Gln.		
		•	· <b>2</b> 2	5 ·		-		230	)		. •	.·	23	5. ,	ja K		
cte	c aa	t ta	c at	c ac	a ga	a ga	a cti	t aga	a 880	cci	t ta	c ag	a aa	c ct	g cct		948
Le	u Ası	n ¹Ty	r Il	e Th	r Gl	u Gl	u Lei	ı Arı	g Ası	n Pro	о Ту	r Ar	g As	n Le	u.Pro		

BRIGHTONIN - MATTERNAS I S

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Leu	Ala	Ile	Ile	Ile	Gly	Ile	Pro	Leu	Val	Thr	Ala	Cys	Tyr	Ile	Leu	
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atg	aac	gtg	tcc	tac	ttc	acc	gtg	atg	act	gcc	acc	gaa	ctc	ctg	cag	1044
Met	Asn	Val	Ser	Tyr	Phe	Thr	Val	Met	Thr	Ala	Thr	Glu	Leu	Leu	Gln	
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Ser	Gln	Ala	Val	Ala	Val	Thr	Phe	Gly	Asp	Arg	Val	Leu	Tyr	Pro	Ala	
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Ser	Trp	Ile	Val	Pro	Leu	Phe	Val	Ala	Phe	Ser	Thr	Ile	Gly	Ala	Ala	
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Glu	Gly	His	Met	Leu	Lys	Val	Leu	Ser	Tyr	Ile	Ser	Val	Arg	Arg	Leu	
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act	cca	gcc	ccc	gcc	atc	atc	ttt	tat	ggt	atc	ata	gca	acg	att	tat	1284
Thr	Pro	Ala	Pro	Ala	Ile	Ile	Phe	Tyr	Gly	Ile	Ile	Ala	Thr	Ile	Tyr	
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					Ile											
				370					375							

	•															
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Ala	Trp	Leu	Phe	Tyr	Gly.	Leu	Thr	Ile	Leu	Gly	Leu	Ile	Val	Met	Arg	
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Phe	Thr	Arg	Lys	Glu	Leu	Glu	Arg	Pro	Ile	Lys	Val	Pro	Val	Val	Ile	
		400					405			•		410	,	4 ÷	. 5	
ccc	gtc	ttg	atg	aca	ctc	atc	tct	gtg	ttt	ttg	ġtt	ctg	gct	cca	atc	1476
Pro	Val	Leu	Met	Thr	Leu	Ile	Ser	Val	Phe	Leu	Val	Leu	Ala	Pro	Ile	
¥.	415					420					425	• 4		• ! •	1	
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Ile	Ser	Lys	Pro	Thr	Trp	Glu	Tyr	Leu	Tyr	Cys	Val	Leu	Phe	Ile	Leu	
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Ala	Gln	Lys	Ile	Ser	Lys	Pro	Ile	Thr	Met	His	Leu	Gln	Met	Leu	Met ·	
:			465	•				470	· ·				475	; · ··		
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Glu	Val	Val	Pro	Pro	Glu	Glu	Asp	Pro	Glu					•.	•	
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Ser	Ser	Leu	Leu	Leu	Ala	Pro	Ala	Leu	Gln	Leu	Leu	Leu	Asp	Thr	Phe	
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Thr	Pro	Cys	Gly	Ala	Leu	Leu	Leu	Pro	Leu	Val	Leu	Pro	G1 y	Asp	Pro-	
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Pro	Ala	Pro	Pro	Arg	Ser	Pro	Leu	Ala	Ala	Leu	Gly	·Leu	Ser	Leu	Phe	

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Ala	Gly	Ala	Val	Gly	Gly	Gly	Ala	Gly	Ala	Arg	Gly	Gly	Arg	Arg	Arg	
				300					305					310		
gag	ctg	ggg	ggg	tcc	cct	gct	ggc	cgc	ggc	tgt	ggc	cta	tgg	gct	gag	1134
Glu	Leu	Gly	Gly	Ser	Pro	Ala	Gly	Arg	Gly	Cys	Gly	Leu	Trp	Ala	Glu	
			315	<i>:</i>				320		٠,		1.	325	,	: ••	ı
cgc	ggg	gag	tta	cgc	ccc	gct	ggt	ttt	cgg	tgt	act	ccc	cgg	gct	ggt	1182
Arg	Gly	Glu	Leu	Arg	Pro	Ala	Gly	Phe	Arg	Cys	Thr	Pro	Arg	Ala	Gly	
ų.	∴ •	330	de de				335				;	340		• I	י	

ggg cgt cgg agg tgt ggt gca ggc cac agg gct ggt gat gat gct gat	. 1230
Gly Arg Arg Arg Cys Gly Ala Gly His Arg Ala Gly Asp Asp Ala Asp	
345	
gag cct cgg ggg gct cct ggg ccc tcc cct gtc agg ctt cct aag gga	1278
Glu Pro Arg Gly Ala Pro Gly Pro Ser Pro Val Arg Leu Pro Lys Gly	
360 365 370 375	
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gggctagcgc gggtttcagc gacgggagcc ctcaagggac atg gca act aca gcg	115
Met Ala Thr Thr Ala	
$eta_{i,j}$ , $eta_{i,j}$	
gog cog gog ggo ggo cga aat gga got ggo cog gaa tgg gga ggg	163

Ala	Pro	Ala	Gly	Gly	Ala	Arg	Asn	Gly	Ala	Gly	Pro	Glu	Тгр	Gly	Gly	
		٠,		10					15					20		
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Phe (	Glu	Glu	Asn	Ile	Gln	Gly	Gly	Gly	Ser	Ala	Val	Ile	Asp	Met	Glu	
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Asn I	Met	Asp	Asp	Thr	Ser	Gly	Ser	Ser	Phe	Glu	Asp	Met	G1y	Glu	Leu	
		40					45			•		50		,		
cat	cag	cgc	ctg	cgc	gag	gaa	gaa	gta	gac	gct	gat	gca	gct	gat	gca	307
His (	Gln	Arg.	Leu	Arg	Glu	Glu	Glu	Val	Asp	Ala	Asp	Ala	Ala	Asp	Ala	
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gct g	gct	gct	gaa	gag	gag	gat	gga	gag	ttc	ctg	ggc	atg	aag	ggc	ttt	355
Ala A	Ala	Ala	Glu	Glu	Glu	Asp	Gly	Glu	Phe	Leu	Gly	Met	Lys	Gly	Phe <sup>-</sup>	
70					75					80					85	
aag g	gga	cag	ctg	agc	cgg	cag	gtg	gca	gat	cag	atg	tgg	cag	gct	ggg	403
Lys (	Gly	Gln	Leu	Ser	Arg	Gln	Val	Ala	Asp	Gln	Met	Trp	Gln	Ala	Gly	
95		••	•	90		-			95					100	-	
aaa a	aga	caa	gcc	tcc	agg	gcc	ttc	agc	ttg	tac	gcc	aac	atc	gac	atc	451
Lys A	Arg	Gln	Ala	Ser	Arg	Ala	Phe	Ser	Leu	Tyr	Ala	Asn	Ile	Asp	Ile	
<b>.</b>		:	105	•				110					115			
ctc a	aga	ссс	tac	ttt	gat	gtg	gag	cct	gct	cag	gtg	cga	agc	agg	ctc	499
Leu A	Arg	Pro	Tyr	Phe	Asp	Val	Glu	Pro	Ala	Gln	Val	Arg	Ser	Arg	Leu	
1- 1	1 34	120					125					130	1		. • •	
																5.40
ctg, g	gag	tcc	atg	atc	cct	atc	aag	atg	gtc	aac	ttc	ccc	cag	aaa	att	547

	135				. ,	140			• •		145				* **	
gca	ggt	gaa	ctc	tat	gga	cct	ctc	atg	ctg	gtc	ttc	act	ctg	gtţ	gct	595
Ala	Gly	Glu	Leu	Tyr	Gly	Pro	Leu	Met	Leu	Val	Phe	Thr	Leu	Val	Ala	
150	:	٠.	. :		155	. *	:			160				•	165	
atc	cta	ctc	cat	ggg	atg	aag	acg	tct	gac	act	att	atc	cgg	gag	ggc	643
Ile	Leu	Leu	His	Gly	Met	Lys	Thr	Ser	Asp	Thr	Ile	Ile	Arg	Glu	Gly	
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Thr	Leu	Met	Gly	Thr	Ala	Ile	Gly	Thr	Cys	Phe	Gly	Tyr	Trp	Leu	Gly	
		٠.	185					190					195		٠	
gtc	tca	tcc	ttc	att	tac	ttc	ctt	gcc	tac	ctg	tgc	aac	gcc	cag	atc	739
Val	Ser	Ser	Phe	Ile	Tyr	Phe	Leu	Ala	Tyr	Leu	Cys	Asn	Ala	Gln	Ile	
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acc	atg	ctg	cag	atg	ttg	gca	ctg	ctg	ggc	tat	ggc	ctc	ttt	ggg	cat	787
Thr	Met	Leu	Gln	Met	Leu	Ala	Leu	Leu	G1y	Tyr	Gly	Leu	Phe	Gly	His	
	215	; <i>.</i>				220					225	i		•		
tgo	att	gto	ctg	tto	atc	acc	tat	aat	atc	cac	ctc	cac	gco	cto	ttc	835
Cys	: Ile	e Val	Leu	. Phe	Ile	Thr	Туг	Asn	Ile	His	Leu	His	Ala	a Let	ı Phe	
230	). <i>'</i> '	; :	:	٠.	235					240	)	٠			. 245	
tad	cto	e ito	c tgg	g ctg	g ttg	gtg	gg1	t gga	ctg	tcc	aca	a ctg	cg	c at	g gta	883
Tyi	r Lei	ц Phe	e Trp	Let	ı Leu	Val	Gl	y Gly	r Leu	Ser	Thi	r Leu	Ar	g Me	t Val	<i>:</i>
	·· . ·	. ;		250	) .	٠.			255	5	٠, .		٠.	· 26	0 "	
gc	a gt	g tt	g gt	g tc	t cgg	gaco	c gt	g gg	c ccc	aca	a ca	g cgg	ct	g ct	c ctc	93
Al	a Va	l Le	u Va	1 Se	r Arg	g Thi	r Va	1 G1;	y Pro	Th	r Gl	n Arg	g Le	u Le	u Leu	•
4.			26	<b>5</b> :		1		270	0	٠.	<b>.</b>		27	5	1.77	

tot our are eta art are eta car	atg ctc ttc ctg ctc tat ctg cat	070
		979
Cys Gly Thr Leu Ala Ala Leu His	Met Leu Phe Leu Leu Tyr Leu His	
280 285	290	
ttt gcc tac cac aaa gtg gta gag	ggg atc ctg gac aca ctg gag ggc	1027
Phe Ala Tyr His Lys Val Val Glu	Gly Ile Leu Asp Thr Leu Glu Gly	
295 300	305	
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Pro Asn Ile Pro Pro Ile Gln Arg	Val Pro Arg Asp Ile Pro Ala Met	
310 315	320 325	
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Leu Pro Ala Ala Arg Leu Pro Thr	Thr Val Leu Asn Ala Thr Ala Lys	
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Ala Val Ala Val Thr Leu Gln Ser	His	
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/212\\ DNA   1		

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<221> CDS						·:	
<222> (80).	(2083)					* ; * * *	
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gcaggagaag	ggccagaga	atg tcg	tcc cag	cca gca g	gg aac cag	acc .tcc	112
,		Met Ser	Ser Gln	Pro Ala G	Gly Asn Gln	Thr Ser	
-)(		1		5		10	
ccc ggg gc	c aca gag	gac tac t	cc tat g	ggc agc tg	gg tac atc	gat gag.	160
Pro.Gly Al	a Thr Glu	Asp Tyr S	Ser Tyr (	Gly Ser Tr	rp Tyr Ile	Asp Glu	
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ccc cag gg	g ggc gag	gag ctc o	cag cca (	gag ggg ga	aa gtg ccc	tcc tgc	208
Pro Gln Gl	y Gly Glu	Glu Leu (	Gln Pro (	Glu Gly G	lu Val Pro	Ser Cys	
3	0		<b>35</b> - ,		40		
cac acc ag	c ata cca	ccc ggc	ctg tac.	cac gcc t	gc ctg gcc	tcg ctg.	256
His Thr Se	r Ile Pro	Pro Gly I	Leu Tyrj	His Ala C	ys Leu Ala	Ser Leu	
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tca atc ct	t gtg ctg	ctg ctc	ctg gcc	atg ctg g	tg agg cgc	cgc.cag	304
Ser Ile Le	eu Val Leu	Leu Leu	Leu; Ala	Met Leu V	al Arg Arg	Arg Gln,	
60		65		70		75	
ctc tgg co	t gac tgt	gtg cgt	ggc agg	ccc ggc c	tg ccc agc	cct gtg	352
Leu Trp Pr	o Asp Cys	Val Arg	Gly Arg	Pro Gly L	eu Pro Ser	Pro; Val;	
	80	ı		85		90 <sub>(1,0,1)</sub>	
gat ttc ti	tg gct ggg	gac agg	ccc cgg	gca gtg c	ct gct gct	gtt.ttc	400

Asp	Phe	Leu	Ala	Gly	Asp	Arg	Pro	Arg	Ala	Val	Pro	Ala	Ala	Val	Phe	
	,		95					100					105			
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Met	Val	Leu	Leu	Ser	Ser	Leu	Cys	Leu	Leu	Leu	Pro	Asp	G1u	Asp	Ala	
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Leu	Pro	Phe	Leu	Thr	Leu	Ala	Ser	Ala	Pro	Ser	Gln	Asp	Gly	Lys	Thr	
-	125			-		130					135					
gag	gct	cca	aga	ggg	gcc	tgg	aag	ata	ctg	gga	ctg	ttc	tat	tat	gct	544
Glu	Ala	Pro	Arg	Gly	Ala	Trp	Lys	Ile	Leu	Gly	Leu	Phe	Tyr	Tyr	Ala	
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gcc	ctc	tac	tac	cct	ctg	gct	gcc	tgt	gcc	acg	gct	ggc	cac	aca	gct	592
Ala	Leu	Tyr	Tyr	Pro	Leu	Ala	Ala	Cys	Ala	Thr	Ala	Gly	His	Thr	Ala	
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Ala	His	Leu	Leu	Gly	Ser	Thr	Leu	Ser	Trp	Ala.	His	Leu	Gly	Val	Gln <sub>,</sub>	
• -			175					180					185	, -		
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Val	Trp	Gln	Arg	Ala	Glu	Cys	Pro	Gln	Val	Pro	Lys	Ile	Tyr	Lys	Tyr	
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tac,	tcc	ctg	ctg	gcc	tcc	ctg	cct	ctc	ctg	ctg	ggc	ctc	gga	ttc	ctg .	736
Tyr	Ser	Leu	Leu	Ala	Ser	Leu	Pro	Leu	Leu	Leu	Gly	Leų	Gly	Phe	Leu	
• •	205,	•			,	210					215				•	
agc	ctt	tgg	tac	cct	gtg	cag	ctg	gtg	aga	agc	ttc	agc	cgt	agg	aca	784
Ser	Leu	Trp	Tyr	Pro	Val	Gln	Leu	Val	Arg	Ser	Phe	Ser	Arg	Arg	Thr	

220				'	225			•	• •	230	•			4.2 °	235 ·	
gga	gca	ggc	tcc	aag	ggg	ctg	cag	agc	agc	tac	tct	gag	gaa	tat	ctg	832
Gly .	Ala	Gly	Ser	Lys	Gly	Leu	Gln	Ser	Ser	Tyr	Ser	Glu	Glu	Týr	Leu	
			t	240					245			•		250	88	
agg	aac	ctc	ctt	tgc	agg	aag	aag	ctg	gga	agc	agc	tac	cac	acc	tcc	880
Arg	Asn	Leu	Leu	Cys	Arg	Lys	Lys	Leu	Gly	Ser	Ser	Tyr	His	Thr	Ser	
		٠٠.	255		•			260		•			265	•		
aag	cat	ggc	ttc	ctg	tcc	tgg	gcc	cgc	gtc	tgc	ttg	aga	cac	tgc	atc	928
Lys	His	Gly	Phe	Leu	Ser	Trp	Ala	Arg	Val	Cys	Leu	Arg	His	Cys	Ile	
	•	270	٠	•			275					280			***	7.1
tac	act	cca	cag	cca	gga	ttc	cat	ctc	ccg	ctg	aag	ctg	gtg	ctt	tca	976
Tyr	Thr	Pro	Gln	Pro	Gly	Phe	His	Leu	Pro	Leu	Lys	Leu	Val	Leu	Ser	
	285					290			٠	• )	295				•	
gct	aca	ctg	aca	ggg	acg	gcc	att	tac	cag	gtg	gcc	ctg	ctg	ctg	ctg	1024
Ala	Thr	Leu	Thr	Gly	Thr	Ala	Ile	Tyr	Gln						Leu	<b>-</b> ·
300	•				305	•				310	٠				315	
gtg	ggc	gtg	gta	ccc	act	atc	cag	aag	gtg	agg	gca	ggg	gigto	acc	acg	1072
Val	Gly	Val	Val	Pro	Thr	Ile	Gln	Lys	Val	Arg	Ala	Gly	Val	Thr	Thr	
٠	. `	• •		320	-	•		•	325	V 4	٠			330	)	
gat	gto	tcc	tac	ctg	ctg	gco	ggo	ttt	gga	atc	gte	cto	tcc	ga <sub>(</sub>	g gac	1120
Asp	Va!	Ser													ı Asp	
-			`338	5" `		•	•	340	) ′ "	•	4.		`34	5 '	and take	
aag	ca	g gag	ggtg	gte	gag	g ct	ggtg	g aag	g cac	cat	cte	g tgg	g gç	t ct	ġ gaa	1168
Lys	Gli	n Glu	ı Val	l Val	l Glu	ı Lei	ı Vai	l Lys	s His	His	Lei	i Tr	o' Ala	a Le	u Glù	
1	· 3 .3	<sup>-</sup> 350	0	٠.		: .	35	5 -	•	1 1	• •	36	0 · .;	(1 ·	12 T 10	

gtg	tgc	tac	atc	tca	gcc	ttg	gtc	ttg	tcc	tec	tta	oto	800	ttc	ctø	1216
101					Ala		Val	Leu	Ser	Cys		Leu		rne		
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Val	Leu	Met	Arg	Ser	Leu	Val	Thr	His	Arg	Thr	Asn	Leu	Arg	Ala	Leu	
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His	Arg	Gly	Ala	Ala	Leu	Asp	Leu	Ser	Pro	Leu	His	Arg	Ser	Pro	His	
				400					405					410		
ccc	tcc	cgc	caa	gcc	ata	ttc	tgt	tgg	atg	agc	ttc	agt	gcc	tac	cag	1360
					Ile											
110	Jei	νπ g			116	1 110	Cys		me c	Jei	1 116	361		lyl	GIII	
	٠		415					420					425			
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Thr	Ala	Phe	Ile	Cys	Leu	Gly	Leu	Leu	Val	Gln	Gln	Ile	Ile	Phe	Phe	
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Leu	Gly	Thr	Thr	Ala	Leu	Ala	Phe	Leu	Val	Leu	Met	Pro	Val	Leu	His	
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Glv	Arg	Asn	Leu	Leu	Leu	Phe	Arg	Ser	Leu	G1u	Ser	Ser	Trp	Pro	Phe	
								•••							475	
														•		4.550
					ctg								_			1552
Trp	Leu	Thr	Leu	Ala	Leu	Ala	Val	Ile	Leu	Gln	Asn	Met	Ala	Ala	His	
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tgg	gtc	ttc	ctg	gag	act	cat	gat	gga	cac	cca	cag	ctg	acc	aac	cgg	1600

Trp	Val	Phe	Leu	Glu	Thr	His	Asp	Gly	His	Pro	Gln	Leu	Thr	Asn	Arg	
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Arg	Val	Leu	Tyr	-Ala-	Ala	Thr	Phe	Leu	Leu	Phe	Pro	Leu	Asn	Val	Leu	
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Val	Gly	Ala	·Met	Val	Ala	Thr	Trp	Arg	Val	Leu	Leu	Ser	Ala	Leu	Tyr	
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Asn	Ala	Ile	His	Leu	Gly	Gln	Met	Asp	Leu	Ser	Leu	Leu	Pro	Pro	Arg	<b>;</b> ;
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gcc	gcc	act	ctc	gac	ccc	ggc	tac	tac	acg	tac	cga	aac	ttc	ttg	aag	1792
Ala	Ala	Thr	Leu	Asp	Pro	Gly	Tyr	Tyr	Thr	Tyr	Arg	Asn	Phe	Leu	Lys	
٠				560					. 565					570	<b>)</b> .	
att	gaa	gto	ago	cag	tcg	cat	cca	gcc	atg	aca	gcc	tto	tgo	tco	ctg	1840
Ile	Glu	Va]	Ser	- Gln	Ser	His	Pro	Ala	Met	Thr	Ala	Phe	e Cys	Ser	Leu	•
٠.			575	5				580	١				585	, ,		
ctc	cts	g caa	a gcg	g cag	ago	ctc	cta	ccc	agg	acc	ate	g gca	a gco	ccc	cag	1888
Leu	Leu	ı Glı	n Ala	a Glr	Ser	Leu	Leu	Pro	Arg	Thr	Met	t Ala	a Ala	a Pro	Gln	
	-	59	0	-			595	;				60	0	* :		
gac	age	c ct	c ag	a cca	ggi	g gag	gaa	gac	gaa	ggg	g at	g ca	g ct	g cta	a cag	1936
Asp	Se:	r Le	u Ar	g Pro	G1;	y Glu	Glı	ı Ası	Glu	ı Gly	y Me	t Gl	n Le	u Le	u Gln	
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															g Gly	

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Gln Val Phe Arg Lys Thr Ala Leu Leu Gly Ala Asn Gly Ala Gln Pro	
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	Met Ile Va	al Cys Leu Leu Pho	e Met Met Ile	
	. 1 .	5 ,	. 10	
tta ttg gca aag gaa	gtt caa ctg gta	a gac caa aca gat	tca cct tta 160	)
Leu Leu Ala Lys Glu	Val Gln Leu Val	l Asp Gln Thr Asp	Ser Pro Leu	
15		20	25	
ctt agt ctc ctt gga	cag aca agc tca	a ctt tca tgg cat	ctt gtg gat 208	3
Leu Ser Leu Leu Gly	Gln Thr Ser Ser	r Leu Ser Trp His	Leu Val Asp	
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attigtg tcg tac cag	agt gtg cta ag	t tat ttc agc agc	cat tac ccg 250	6
Ile Val Ser Tyr Gln	Ser Val Leu Se	r.Tyr Phe Ser Ser	His Tyr Pro	
45	. 50		o .	
ccg tcc atc atc ctg	gca aaa gaa tc	t tat gct gaa tta	atc atg aag 30	4
Pro Ser Ile Ile Leu	Ala Lys Glu Se	r Tyr Ala Glu Leu	Ile.Met Lys	
60	65	70		
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Leu Leu Lys Val Ser				
75	80	85	90	
cat ctt gat gca gtt	cca aaa tgc ca	a get ttt act cat	cag atgigtt 40	0
His Leu Asp Ala Val				
95		100	105 🔀	
30				

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cta	gaa	cag	gaa	atg	tct	aag	ctc	tta	gac	gat	atc	att	gtc	ttt	aac .	496
Leu	Glu	G1n	Glu	Met	Ser	Lys	Leu	Leu	Asp	Asp	Ile	Ile	Val	Phe	Asn	
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Pro	Pro	Asp	Met	Asp	Ser	Gln	Thr	Arg	His	Met	Ala	Leu	Ser	Ser	Leu	
	140					145					150				•	
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Gly	Leu	Val	Val	Leu	Pro	Leu	Leu	Thr	Ala	Ala	Cys	Gln	Ser	Leu	Ala .	
•	•	٠	190	•	÷			195			•		200	٠.	-	
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Ser	Val	Arg	His	Met	Ala	Glu	Thr	Thr	Glu	Ala	Cys	Ile	Thr	Ala	Tyr	
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:	٠		• •	255			4		260					265	٠	,
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Cys	Leu	Asn	Ser	Glu	Gln	Thr	Leu	Arg	Asn	Glu	Met	Lys	Val	Leu	Leu	
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Glu	Ala	Lys	Leu	Phe	Leu	Trp	Trp	His	Gln	Val	Leu	G1n	Leu	Ser	Leu	. •
:	300	١	•			305					310	-				
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٠.	٠	17.		33	5	•			340	) '				34	5	• 1
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Lei	Se:	r Se	r Gl	y Il	e Le	u Gl	y Ala	a Il	e Gl	y Ph	e Gl	y Ar	g Ly	s Se	r Pro	<b>o</b> :
ï		:	35	0.		٠.		35	5 .	·. •		•	36	0 '		·
ttį	g tc	t aa	c ag	g tt	c cg	a gt	g gt	t gc	c cg	a ag	c at	g gc	t go	c tt	c ct	t 1216
Lei	u <sup>:</sup> Se	r As	n Ar	g Ph	e Ar	g Va	l Va	1 A1	a Ar	g Se	r Me	t Al	a Al	a Pł	ne Le	u
4.3	:	<sup>2</sup> ·36	55	, , ,			37	0	••.	. '	Ç +	37	<b>'</b> 5	•	30.0	11

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Tyr	Leu	Asp	His	Ile	Arg									В	i	•
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145					150											588
															tac	500
Ala	Ser	Ser	Gly	Ala	Thr	Phe									y Tyr	
	٠			. 165				•		) •						000
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Thr	Thr	Ala	a Asr	n Ala	Glu	ı Ser	Asp	Asn	Glu	ı Arg	, Asp	Sei	. Ası	Lys	s Glu	
	. · ·		180	) (	•		•	185	5 .				190	) ·· .	-i.a	
agt	; gag	g ga	ggi	g gaa	a gat	t gaa	i gtg	ago	tg1	t gag	act	gt	g aa	g at	g ggg	684
Sea	- Glu	ı Ası	p G1	y Glu	ı Ası	o Glu	ı Val	Sei	c Cy:	s Glu	ı Thr	. Va	l Ly:	s Me	t Gly:	
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ag	a aa	g ga	t tc	t ct	t ga	c tt	g gag	g ga	a ga	g gca	a gc1	t tc	a gg	t gc	c tcc·	732
Ar	g Ly:	s As	p Se	r Le	u As	p Lei	u Glu	ı Gl	u Gl	u Ala	a Ala	a Se	r Gl	y Al	a: Ser.,	
	c. 91	n .	, -	1 4		21	5 ·			-	220	0	Ŋ	, · · ·	60 3 20	

agt	gcc	ctg	gag	gct	gga	ggt	tcc	tca	ggc	ttg	gag	gat	gtg	ctg	ccc	780
Ser	Ala	Leu	Glu	Ala	Gly	Gly	Ser	Ser	Gly	Leu	Glu	Asp	Val	Leu	Pro	
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Met Glu Gln Gly Ser Gly Arg Leu Glu Asp Phe Pro	
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Val Asn Val Phe Ser Val Thr Pro Tyr Thr Pro Ser Thr Ala Asp Ile	
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Gln	Val	Ser	Asp	Asp	Asp	Lys	Ala	Gly	Ala	Thr	Leu	Leu	Phe	Ser	Gly	
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Ile	Phe	Leu	Gly	Leu	Val	Gly	Ile	Thr	Phe	Thr	Val	Met	Gly	Trp	Ile	
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Lys	Tyr	G1n	Gly	Val	Ser	His	Phe	Glu	Trp	Thr	Gln	Leu	Leu	Gly	Pro	
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Val	Leu	Leu	Ser	Val	Gly	Val	Thr	Phe	Ile	Leu	Ile	Ala	Val	Cys	Lys	
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Phe	Lys	Met	Leu	Ser	Cys	Gln	Leu	Cys	Lys	Glu	Ser	Glu	Glu	ı Arı	g Val	
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Pro	Asp	Sea	r Glu	ı Glm	Thr	Pro	Gly	Gly	Pro	Ser	Phe	e Val	l Phe	e Th	r Gly	
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Ile	e Ası	n Gl	n Pr	o Ile	e Thi	r Phe	e His	s Gly	, Ala	a Thi	r Va	l Va	1 G1	n Ty	r Ile	•
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cc	t cc	t cc	t 'ta	t gg	t tc	t cc	a ga	g cc	t at	g gg:	g at	a aa	t ac	c ag	c tac	541
Pr	o Pr	o Pr	о Ту	r Gl	y Se	r Pr	o Gl	u Pr	o Me	t Gl	y 'Il	e As	n Th	r Se	er Ty	r
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ct	g ca	g to	t gt	ggt	g ag	c cc	c tg	c gg	c ct	c at	a ac	c to	t gg	ga gg	gg gc	a 589

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Ala	Ala	Ala	Met	Ser	Ser	Pŗo	Pro	Gln	Tyr	Tyr	Thr	Ile	Tyr	Pro	Gln	
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Gln	Leu	Glu	Glu	Glu	Ala	Cys	Ala	Cys	Phe	Ser	Pro	Pro	Pro	Tyr	Glu	
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was a commence

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Gln Gln Leu Glu Leu Asp Glu Asp Glu Ala Ser Cys Cys Arg Trp Gly	
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Leu	Pro	Ile	Val	Gly	Lys	Ala	Phe	Ile	Arg	Pro	Phe	Arg	Glu	His	His	
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Phe	Arg	Thr	His	Ser	Pro	Glu	Ala	Leu	Glu	Gln	Leu	Tvr	Pro	Trp	Glu	

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Cys	Phe	Val	Phe	Cys	Leu	Ile	Ile	Phe	Gly	Thr	Phe	Thr	Asn	G1n	Ile	
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cac	aag	tgg	tcg	cac	acg	tac	ttt'	ggg	ctg	cca	cgc	tgg	gtc	acc	ctc	689
His	Lys	Trp	Ser	His	Thr	Tyr	Phe	Gly	Leu	Pro	Arg	Trp	Val	Thr	Leu	
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Leu	Gln	Asp	Trp	His	Val	Ile	Leu	Pro	Arg	Lys	His	His	Arg	Ile	His	
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Ala	Gln	Lys	Ile	Lys	;	٠								: :	* 2007	
٠.			٠.	270	)					. ,		٠.	:	٠, ،	1 •	
tto	ccta	gcc	ccca	aacc	ga a	gcca	tctg	c ca	aatt	.ccag	cct	cttt	gag	ctgg	gcccctc	990
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Tyr	Tyr	Phe	Leu	Lys	Arg	Tyr	Phe	Gly	Ser	Thr	Val	Ala	Phe	Leu	Asn	
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Leu	Trp	Thr	Ser	Leu	Phe	Leu	Gly	Ser	Gly	Val	Val	Ala	Gly	Gln	Ala	
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Leu	Leu	Leu	Ala	Glu	Tyr	Ser	Ile	Gln	Pro	Phe	Phe	Pro	Ser	Cys	Ser	
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Val	Pro	Lys	Leu	Pro	Lys	Lys	Cys	Leu	Ala	Leu	Ala	Met	Leu	Trp	Ile	
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Ile	Ala	Ser	Ser	Val	Leu	Lys	Val	Ser	Ile	Leu	Ser	Phe	Ile	Ser	Leu	
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Thr	Gly	Val	Val	Phe	Leu	Ile	Arg	Gly	Lys	Lys	Glu	Asn	Val	Glu	Arg	
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Phe	Gln	Asn	Ala	Phe	Asp	Ala	Glu	Leu	Pro	Asp	Ile	Ser	His	Leu	Ile	
d.	•	195					200			<b>.</b> :		205		,	- <i>:</i> ;	,
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Pro	Arg	Thr	Thr	Ile	Pro	Lys	Cys	Ile	Phe	Thr	Ala	Leu	Pro	Leu	Val	
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Thr	Val	Val	Tyr	Leu	Leu	Val	Asn	Ile	Ser	Tyr	Leu	Thr	Val	Leu	Thr	
:	,			245	٠.	. đ			250	9		.: 7	r .	255	· ,	

Pro	Arg	Glu	Ile	Leu	Ser	Ser	Asp	Ala	Val	Ala	Ile	Thr	Trp	Ala	Asp
	. •	÷	260					265					270		
Arg	Ala	Phe	Pro	Ser	Leu	Ala	Trp	Ile	Met	Pro	Phe	Ala	Ile	Ser	Thr
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Ser	Leu	Phe	Ser	Asn	Leu	Leu	Ile	Ser	Ile	Phe	Lys	Ser	Ser	Arg	Pro
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Cys Leu Ser	Ala	Arg	Asp	Gly	Ser	Årg	Met	Leu	Leu	Leu	Leu	Leu	Leu
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Gly Thr Gly	Ser	Ser	Ser	Leu	Trp	Asn	Leu	Met	Gly	Asn	Ala	Met	Val
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Met Thr Gln	Tyr	Ile	Arg	Leu	Thr	Pro	Asp	Met	Gln	Ser	Lys	Gln	Gly
		85					90					95	•
Ala Leu Trp	Asn	Arg	Val	Pro	Cys	Phe	Leu	Arg	Asp	Trp	Glu	Leu	Gln
	100					105					110		. •
Val His Phe	Lys	Ile	His	Gly	Gln	Gly	Lys	Lys	Asn	Leu	His	Gly	Asp
115					120					125	;		:
Gly Leu Ala	Ile	Trp	Tyr	Thr	Lys	Asp	Arg	Met	Gln	Pro	Gly	Pro	Val
130				135					140	, ,	٠,	•	. : .
Phe Gly Asn	Met	. Asp	Lys	Phe	Val	Gly	Leu	Gly	Val	Phe	Val	Asp	Thr
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Tyr Pro Asr	Glu	ı Glu	ı Lys	Gln	Gln	Glu	ı Arg	Val	Phe	Pro	Туг	· Ile	Ser
		165	5				170	)				175	; : :
Ala Met Val	l Asr	n Ası	ı Gly	/ Ser	. Leu	. Ser	Туг	. Asp	His	s Glu	ı Arg	g Asp	Gly
	180	)				188	5				190	) '	•
Arg Pro Thi	r Gli	u Lei	u G1;	y Gly	y Cys	s Thi	r Ala	a Ile	e Va	l Ar	g Ası	n Lei	ı His
νώ τι <b>`19</b> !	5	Ez .	.,, .		200	)		<del>.</del> '	.* .	20	5	' ; n	( ) (6)

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Pro Gly Val Arg Leu Pro Arg Gly Tyr Tyr Phe Gly Thr Ser Ser Ile	;
245 250 255	
Thr Gly Asp Leu Ser Asp Asn His Asp Val Ile Ser Leu Lys Leu Phe	:
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Glu Leu Thr Val Glu Arg Thr Pro Glu Glu Glu Lys Leu His Arg Asp	,
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Pro Leu Pro Pro Leu Ser Gly Leu Ala Leu Phe Leu Ile Val Phe Phe	
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Asn Lys Trp Gln Glu Gln Ser Arg Lys Arg Phe Tyr	
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Ser	Ser	Asn	Ser	Thr	Gly	Val	Leu	Glu .	Ala	Ala	Asn	Asn	Ser	Leu	Val
		٠,	·20	. •			-	25					30	• .•	Estate 19
Val	Thr	Thr	Thr	Lys	Pro	Ser	Ile	Thr	Thr	Pro	Asn	Thr	Glu	Ser	Leu
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Pro	Asn	Ala	val	Ser	Thr	Leu	Gln	Ser	Ser	Lys	Pro	Lys	Thr	Glu	Thr
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G1n	Ser	Sez	r Ile	Lys	Thr	Thr	Glu	Ile	Pro	G1 y	Ser	- Val	Leu	Glm	Pro
	130	)				135					140	,	٠	•. •	
Asp	Ala	a Ser	r Pro	Se1	Lys	Thr	Gly	Thr	Leu	Thi	Ser	r Ile	e Pro	Va]	Thr
145	5				150	)				159	5				160
Ile	e Pro	o Gl	u Ası	n Thi	r Ser	Glr	ı Ser	Gln	Val	Ile	e G1;	y Thi	r Glu	ı Gly	Gly
				16	5				170	)				17	5 👯 😘
Lys	s As	n Al	a Se	r Th	r Sei	r Ala	a Thi	Ser	Arg	g Se:	r Ty	r Se			e Ile
			18	0				185	5			•	19	0	• 51
Lei	u Pr	o Va	l Va	1 II	e Ala	a Le	u Il	e Val	Ile	e Th	r Le	u Se	r Va	1 Ph	e Val
٠.	<u>.</u>	- 19	5		ur v.		. 20	0	د	: ,		20	5	· : ·	1. 1 A.

Leu	Val	Gly	Leu	Tyr	Arg	Met	Cys	Trp	Lys	Ala	Asp	Pro	Gly	Thr	Pro
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Glu	Asn	Gly	Asn	Asp	Gln	Pro	Gln	Ser	Asp	Lys	Glu	Ser	Val	Lys	Leu
225	-:	.· ·			230		-			235					240
Leu	Thr	Val	Lys	Thr	Ile	Ser	His	Glu	Ser	Gly	Glu	His	Ser	Ala	Gln
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Gly	Lys	Thr	Lys	Asn	•										
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Cys	Gln	Pro	Gly	Ala	Glu	Asn	Ala	Phe	Lys	Val	Arg	Leu	Ser	Ile	Arg
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Thr	Ala	Leu	Gly	Asp	Lys	Ala	Tyr	Ala	Trp	Asp	Thr	Asn	Glu	Glu	Tyr
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Leu	Phe	Lys	Ala	Met	Val	Ala	Phe	Ser	Met	Arg	Lys	Val	Pro	Asn	Arg
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Glu	Ala	Thr	Glu	Ile	Ser	His	Val	Leu	Leu	Cys	Asn	Val	Thr	Gln	Arg
<b>65</b> .	. : .,	•			70					75	-		. ,		80
Val	Ser	Phe	Trp	Phe	Val	Val	Thr	Asp	Pro	Ser	Lys	Asn	His	Thr	Leu

	\$ 15 m	*	•	85	.*				90					95		
Pro	Ala	Val	Glu	Val	Gln	Ser	Ala	Ile	Arg	Met	Asn	Lys	Asn	Arg	Ile	
	: *		100	•				105	•		•	•	110	ì		
Asn	Asn	Ala	Phe	Phe	Leu	Asn	Asp	Gln	Thr	Leu	Glu	Phe	Leu	Lys	Ile	
		115				٠.	120		٠.			125	•			
Pro	Ser	Thr	Leu	Ala	Pro	Pro	Met	Asp	Pro	Ser	Val	Pro	Ile	Trp	Ile	
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Ιlε	: Ile	Phe	Gly	Val	Ile	Phe	Cys	Ile	Ile	Ile	Val	Ala	Ile	Ala	Leu	
145					150					155					160	
Let	ı Ile	e Leu	Ser	Gly	Ile	Trp	Gln	Arg	Arg	Arg	Lys	Asn	Lys	Glu	Pro	
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Set	r Glu	ı Val	Asp	Asp	Ala	Glu	Asp	Lys	Cys	Glu	Asn	Met	Ile	Thr	Ile	
			180					185					190		. •	
Gl	u Ası	n Gly	, Ile	e Pro	Ser	Asp	Pro	Leu	Asp	Met	Lys	Gly	Gly	His	Ile	
	٠.	198					200					205				
As	n As	p Ala	a Phe	e Met	: Thr	Glu	. Asp	Glu	Arg	g Leu	Thr	Pro	Leu	l		
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															r Phe	
															<b>5</b> 1	

Ile Leu Leu Ser Gly Thr Arg Cys Glu Glu Asn Cys Gly Asn Pr	o Glu
20 25 30	
His Cys Leu Thr Thr Asp Trp Val His Leu Trp Tyr Ile Trp Le	u Leu
35 40 45	- •
Val Val Ile Gly Ala Leu Leu Leu Leu Cys Gly Leu Thr Ser Le	u Cys
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Phe Arg Cys Cys Leu Ser Arg Gln Gln Asn Gly Glu Asp Gl	y Gly
65 70 75	80
Pro Pro Pro Cys Glu Val Thr Val Ile Ala Phe Asp His Asp Sen	. Thr
85 90 99	5
Leu Gln Ser Thr Ile Thr Ser Leu Gln Ser Val Phe Gly Pro Ala	Ala
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Arg Arg Ile Leu Ala Val Ala His Ser His Ser Ser Leu Gly Glr	Leu
115 120 125	
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Ser Arg Phe Thr Val Ala Met Cys Gly Gln Lys Ala Pro Asp Leu	Pro
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1		: .		. 5			٠	٠	10	٠.	٠.		•	· 15	: .	
Lys	Ser	Ile	Leu	Ser	Ser	Lys	Pro	Ala	Ile	Gly	Ser	Lys	Ala	Val	Asn	
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Pro	Ту	r Gly	Asp	Gln	Arg	Leu	Lys	Pro	Lys	His	Thr	Lys	Leu	Phe	Val	
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Phe	Le	u Ala	a Val	Leu	Ile	Cys	Leu	Val	Thr	Ser	Ser	Phe	Ile	Val	Phe	
	-		100	)				105	i		•		- 110			
Phe	. Le	u Pho	e Pro	Arg	Ser	· Val	Ile	. Val	Gln	Pro	Ala	Gly	Leu	Asn	Ser	
-		· 11	5		. •		120	) ·				125	;			,
Sei	- Th	r Va	l Ala	a Phe	Asp	Glu	ı Ala	a Asp	Ile	Tyı	: Leu	ı Asr	ı Ile	: Thr	Asn	
	13	0				135	5				140	)		1 :	i e e	
Ile	e Le	u As	n Il	e Sei	r Ası	n Gly	, Ası	n Ty	r Tyı	r Pro	o Ile	e Met	t Val	Thr	Gln	
14	5				150	0				15	5				160	
Le	u Th	ır Le	u Gl	u Va	l Le	u Hi:	s Le	u Se	r Lei	u Va	l Va	1 G1:	y Gl	n Val	l Ser	
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Asn	Asn	Leu	Leu	Leu	His	Ile	Gly	Pro	Leu	Ala	Ser	Glu	G1n	Met	Phe
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Thr	Trp	Leu	Glu	Ile	Lys	Val	His	His	Val	Leu	Leu	His	Ile	Gln	Gly
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Thr	Leu	Thr	Cys	Ser	Tyr	Leu	Ser	His	Ser	Glu	Gln	Leu	Val	Phe	Gln
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Ser	Tyr	Glu	Tyr	Val	Asp	Cys	Arg	Gly	Asn	Ala	Ser	Val	Pro	His	Gln
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1			•	5					10				_	15	
Leu	Leu	Phe	Ala	Leu	Phe	Leu	Ala	Ala	Ser	Leu	Gly	Lys	Asp	Ala	Pro
	;; •	٠٠ :	. 20				. •	25					30		
						Pro									
;;	el o	35					40				•	45			
															Cys

BRIEDOCIO - MO 11366043 1 -

50				· 55	: .	-		•	60	. •				
Leu Pro Leu	Ile	Leu	Leu	Leu	Val	Tyr	Lys	Gln	Arg	Gln	Ala	Ala	Ser	
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Asn Arg Arg	Ala	Gln	Glu	Leu	Val	Arg	Met	Asp	Ser	Asn	Ile	Gln	Gly	
		85	. •		,		90			···		95	1.7	
Ile Glu Asn	Pro	Gly	Phe	Glu	Ala	Ser	Pro	Pro	Ala	Gln	Gly	Ile	Pro	
•	100					105					110		•	•
Glu Ala Lys	Val	Arg	His	Pro	Leu	Ser	Tyr	Val	Ala	Gln	Arg	Gln	Pro	
115			•		120					125			9.	•
Ser Glu Ser	Gly	Arg	His	Leu	Leu	Ser	Glu	Pro	Ser	Thr	Pro	Leu	Ser	
130				135					140			,		
Pro Pro Gly	Pro	Gly	Asp	Val	Phe	Phe	Pro	Ser	Leu	Asp	Pro	Val	Pro	
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Asp Ser Pro	Asn	Phe	Glu	Val	Ile								.71	
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Met Ser Sei	r Gly	y Thr	Glu	ı Lei	ı Let	Tr	Pro	Gly	Ala	a Ala	ı Lei	ı Lev	ı Val	Ì
1		. (	5				10	) .		~		15	5 .	·
Leu Leu Gl	y Va	l Ala	a Ala	s Sei	r Lei	і Су	s Va	l Ar	g Cy:	s Sei	r Arı	g Pro	Gl	y
ethic form	2	0 ·			:	. 2	5		··		30	0	·	200

Ala	Lys	Arg	Ser	Glu	Lys	Ile	Tyr	Gln	Gln	Arg	Ser	Leu	Arg	Glu	Asp
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Gln	Gln	Ser	Phe	Thr	Gly	Ser	Arg	Thr	Tyr	Ser	Leu	Val	Gly	Gln	Ala
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Trp	Pro	Gly	Pro	Leu	Ala	Asp	Met	Ala	Pro	Thr	Arg	Lys	Asp	Lys	Leu
65					70					75					80
Leu	Gln	Phe	Tyr	Pro	Ser	Leu	Glu	Asp	Pro	Ala	Ser	Ser	Arg	Tyr	Gln
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Asn	Phe	Ser	Lys	Gly	Ser	Arg	His	Gly	Ser	Glu	Glu	Ala	Tyr	Ile	Asp
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Pro	Ile	Ala	Met	Glu	Tyr	Tyr	Asn	Trp	Gly	Arg	Phe	Ser	Lys	Pro	Pro
	,	115					120					125			
Glu	Asp	Asp	Asp	Ala	Asn	Ser	Tyr	Glu	Asn	Val	Leu	Ile	Cys	Lys	Gln
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Lys	Thr	Thr	Glu	Thr	Gly	Ala	Gln	Gln	Glu	Gly	Ile	Gly	Gly	Leu	Cys
145	•	-			150				,	155				:	160
Arg	Gly	Asp	Leu	Ser	Leu	Ser	Leu	Ala	Leu	Lys	Thr	Gly	Pro	Thr	Ser
	•			165					170					175	
Gly	Leu	Cys	Pro	Ser	Ala	Ser	Pro	Glu	Glu	Asp	Glu	Glu	Ser	Glu	Asp
١.		··.	180	•				185				:	190		٠.
Tyr	Gln	Asn	Ser	Ala	Ser	Ile	His	Gln	Trp	Arg	Glu	Ser	Arg	Lys	Val
~ 1	. ر اندی	195	**	•			200				•,	205	; ·	. •	··
Met	Gly	Gln	Leu	Gln	Arg	Glu	Ala	Ser	Pro	Gly	Pro	Val	Ģly	Ser	Pro
•	· 210	·	ι	4 ti	۲.	215	•			•	. 220		٠,		•
Asp	Glu	Glu	Asp	Gly	Glu	Pro	Asp	Tyr	· Val	Asr	Gly	Glu	ı Val	·Ala	Ala

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Glu	Pro	Arg	Lys	Glu	Ile	Val	Leu	Phe	Asp	Lys	Pro	Thr	Arg	Gly	Thr
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Thr	Val	Gln	Lys	Phe	Lys	Glu	Met	Val	Tyr	Ser	Leu	Phe	Lys	Ala	Lys
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Leu	Gly	Asp	Gln	Gly	Asn	Leu	Ser	Glu	Leu	Val	Asn	Leu	Ile	Leu	Thr
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Ser	Ala	Trp	Ala	Leu	Leu	Gln	Leu	Asn	Glu	Phe	Leu	Leu	Met	Val	Ile
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Leu	Pro	Trp	Val	Ile	Glu	Leu	Phe	Ile	Pro	Ser	Gly	Phe	Arg	Arg	Ser
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Met	Asp	Gln	Leu	Phe	Thr	Pro	Ser	Trp	Pro	Arg	Lys	Ala	Lys	Ile	Ala
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Ile	Gly	Leu	Leu	Glu	Phe	Val	Glu	Asp	Val	Phe	His	Gly	Pro	Tyr	Gly
	se ,	275					280					285			
Asn	Phe <sub>:</sub>	Leu	Met	Cys	Asp	Thr	Ser	Ala	Lys	Asn	Leu	Gly	Tyr	Asn	Asp
٠.	290	:	. ;•			295			· ·		300				
													Pro		
305	. <i>:</i> ·	,; -		(e)	310	٠.				315			· .		320
													Asn		

* * * * * * * * * * * * * * * * * * * *	325		330	335	
Cys Val Tyr G	ly Thr Asp C	ys Arg Th	ar Ser Cys Asp	Gln Ser Thr Met	
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Lys Cys Thr So	er Glu Val I	le Gln Pr	o Asn Leu Ala	Lys Ala Cys Gln	
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Leu Leu Lys A	sp Tyr Leu L	eu Arg G	ly Ala Pro Sei	Glu Ile Arg Glu	
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Glu Leu Glu L	ys Gln Leu 1	Tyr Ser C	ys Ile Ala Leu	Lys Val Thr Ala	
385	390		395	400	
Asn Gln Met G	lu Met Glu H	His Ser L	eu Ile Leu Ası	n Asn Leu Lys Thr	
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1	. 5		10	St. 7 - 115 1	•
Gly Ala Gln	Lys Ala Ala	Leu Val I	Leu Leu Ser Al	a Cys Leu Val Thr	•
	20		25	30	٠.
Leu Trp Gly	Leu Gly Glu	Pro Pro	Glu His Thr Lo	eu Arg Tyr Leu Val	ι,
···· ·· 35		40	:	45	• •

Leu	His	Leu	Ala	Ser	Leu	Gln	Leu	Gly	Leu	Leu	Leu	Asn	Gly	Val	Cys
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Tyr	Trp	Arg	Thr	Val	Arg	Ala	Cys	Leu	Gly	Cys	Pro	Leu	Arg	Arg	Gly
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Ala	Leu	Leu	Leu	Leu	Ser	Ile	Tyr	Phe	Tyr	Tyr	Ser	Leu	Pro	Asn	Ala
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Ser	Ala	Val	Cys	Glu	Lys	Gly	Asn	Phe	Asn	Val	Ala	His	Gly	Leu	Ala
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Trp	Ser	Tyr	Tyr	Ile	Gly	Tyr	Leu	Arg	Leu	Ile	Leu	Pro	Glu	Leu	Gln
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Ser.	Asn.	Ser	Ile	Tyr	Glu	Leu	Leu	Glu	Asn	Gly	Gln	Arg	Asn	Leu	G1n

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#### 155/307

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#### 156/307

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Section 1986 Statement

#### 162/307

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Lys	Pro	Tyr	Gln	Gly	Val	Gly	Thr	Gly	/ Ser	Ser	Ser	Leu	Trp	Asr	ı Leu		
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Me	t Gly	y Ası	n Ala	a Met	: Val	l Met	t Thi	r Glı	n Ty	r Ile	e Ar	g Lei	u Thi	r Pro	o Asp		

75			-		80					85	;				. 90	
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Arg	Asp	Trp	Glu	Leu	Gln	Val	His	Phe	Lys	Ile	His	Gly	Gln	G1y	Lys	
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Val	Phe	Pro	Tyr	Ile	Ser	Ala	Met	Val	Asn	Asn	Gly	Ser	Leu	Ser	Tyr	
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Asp .	His	Glu	Arg	Asp	G1 y	Arg	Pro	Thr	Glu	Leu	Gly	Gly	Cys	Thr	Ala	
٠ <u>٠</u> ٠	• • :		190		·· ·	٠.		195	•	. •	•	٠	200		• •	
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Ile-	Val	Arg	Asn	Leu	His	Tyr	Asp	Thr	Phe	Leu	Val	Ile	Arg	Tyr	Val	
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rne	•	inr	Ser .		116	Thr	GLY	иsр		Ser	vsh	VPII	1112			
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Ile	Ser	Leu	Lys	Leu	Phe	Glu	Leu	Thr	Val	Glu	Arg	Thr	Pro	Glu	Glu	
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Glu	Lys	Leu	His	Arg	Asp	Val	Phe	Leu	Pro	Ser	Val	Asp	Asn	Met	Lys	
·	٠.	285					290					295			• • •	
ctg	cct	gag	atg	aca	gct	cca	ctg	ccg	ccc	ctg	agt	ggc	ctg	gcc	ctc	963
						Pro										
Leu		oru	INC C		A10		Deu			200			200			
•	300					305		ŕ			310				• :	
ttc	ctc	atc	gtc	ttt	ttc	tcc	ctg	gtg	ttt	tct	gta	ttt	gcc	ata	gtc	1011
Phe	Ľeu	Tle	Val	Phe	Phe	Ser	Leu	Val	Phe	Ser	Val	Phe	Ala	Ile	Val	
315				٠.	320		•			325			-		330	
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Ile	Gly	Ile	Ile	Leu	Tyr	Asn	Lys	Trp	Gln	Glu	Gln	Ser	Arg	Lys	Arg	
•;	<i>:</i>			335			ų.		340			. •:		345		
++^	+20	taa	ac c	ctcc	tact	ם רר	acca	cttt	tøt	gact	øtc	accc	atga	gg		1110

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#### 169/307

Phe Tyr

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⟨210⟩ 83

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Glu	Leu	Leu	Gln	Val	Thr	Ile	Leu	Phẹ	Leu	Leu	Pro	Ser	Ile	Cys	Ser	
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Ser	Asn	Ser	Thr	Gly	Val	Leu	Glu	Ala	Ala	Asn	Asn	Ser	Leu	Val	Val	
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Lys	Asn	Val	Val	Thr	Pro	Thr	Thr	Gly	Thr	Thr	Pro	Lys	Gly	Thr	Ile	
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acc	aat	gaa	tta	ctt	aaa	atg	tct	ctg	atg	tca	aca	gct	ąct	tťt	tta	297
Thi	- Asr	Glu	Leu	Leu	Lys	Met	Ser	Leu	Met	Ser	Thr	Ala	Thr	Phe	Leu	
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Asn	Asp	Ser	Ile	Ile	Ser	Asn	Val	Thr	Val	Thr	Ser	Val	Thr	Leu	Pro	
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Asn	Ala	Val	Ser	Thr	Leu	G1n	Ser	Ser	Lys	Pro	Lys	Thr	Glu	Thr	Gln	
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agt	tca	att	aaa	aca	aca	gaa	ata	cca	ggt	agt	gtt	cta	caa	cca	gat	489
Ser	Ser	Ile	Lys	Thr	Thr	Glu	Ile	Pro	Gly	Ser	Val	Leu	Gln	Pro	Asp	
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Ala	Ser	Pro	Ser	Lys	Thr	Gly	Thr	Leu	Thr	Ser	Ile	Pro	Val	Thr	Ile	
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Asn	Ala	Ser	Thr	Ser	Ala <sup>.</sup>	Thr	Ser	Arg	Ser	Tyr	Ser	Ser	Ile	Ile	Leu	
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Asn Gly Asn Asp Gln Pro Gln Ser Asp Lys Glu Ser Val Lys Leu Leu	
230 235 240	
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Thr Val Lys Thr Ile Ser His Glu Ser Gly Glu His Ser Ala Gln Gly	
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Lys Thr Lys Asn	
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Wash of the Grade

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Thr Ala Ile	His Ala (	Glu Leu Cys	Gln Pro	Gly Ala	Glu Asn	Ala Phe	
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aaa gtg aga	ctt agt a	itc aga aca	gct ctg	gga gat	aaa gca	tat gcc	148
Lys Val Arg	Leu Ser 1	le Arg Thr	Ala Leu	Gly Asp	Lys Ala	Tyr Ala	
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Trp Asp Thr	Asn Glu G	lu Tyr Leu	Phe Lys	Ala Met	Val Ala	Phe Ser	
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Met Arg Lys	Val Pro A	sn Arg Glu	Ala Thr	Glu Ile	Ser His	Val Leu	
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Leu Cys Asn	Val Thr G	ln Arg Val	Ser Phe	Trp Phe	Val Val	Thr Asp	
75 ; • .		- 80		85	er a ,	• 8 •	
cct tca aaa	aat cac a	cc ctt cct	gct gtt	gag gtg	caa tca	gcc ata	340
Pro Ser Lys	Asn His T	hr Leu Pro	Ala Val	Glu Val	Gln Ser	Ala Ile	
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Arg	Met	Asn	Lys	Asn	Arg	Ile	Asn	Asn	Ala	Phe	Phe	Leu	Asn	Asp	Gln		
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Ile	Ile	Val	Ala	Ile	Ala	Leu	Leu	Ile	Leu	Ser	Gly	Ile	Trp	Glr	n Arg		
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Cys	s Glu	u As	n Me	t Ile	e Thi	r Il	e Glu	ı Ası	ı Gly	, Ile	e Pro	o Se	r As	p Pr	o Leu		
		•	٠.	190	)				19	5		٠		20	0 .		
ga	c at	g aa	g <b>g</b> g	a gg	g ca	t at	t aa	t ga	t gc	c tt	c at	g ac	a ga	g ga	t gag	676	ò
As	p Me	t Ly	s Gl	y Gl	y Hi	s Il	e As	n As	p Ala	a Ph	e Me	t Th	r Gl	u As	p Glu		
	<i>- :</i>		20	5				21	0 -		•		21	.5		•	
ag	g ct	c ac	c cc	t ct	c tg	aagg	gct	gttg	ttct	gc t	tcct	caag	ga aa	ttaa	acat	73	0
Ar	g Le	u Tł	ır Pı	o Le	u		••						و				
	٠.	22	20			<b>.</b>		٠,				:		2	\$ · ·	•	
++	 afti	rctei	t øts	zacte	ctg	agca	atcct	ga a	atac	caag	ga go	caga	tcata	a ta	ttttg	ttt 79	0

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Leu Leu Tyr Phe Ile Leu Leu Ser Gly Thr Arg Cys Glu Glu Asn Cys

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His	Asp	Ser	Thr	Leu	Gln	Ser	Thr	Ile	Thr	Ser	Leu	Gln	Ser	Val	Phe	
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Gly	Pro	Ala	Ala	Arg	Arg	Ile	Leu	Ala	Val	Ala	His	Ser	His	Ser	Ser-	
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Ala	Leu	His	Met	Ser	Arg	Phe	Thr	Val	Ala	Met	Cys	Gly	Glr	Lys	s-Ala	
. س				-145	; · ·		·· .	н ж	· 150	)				· 155	5 · 1 · 1 · 5	

cct	gat	cta	ccc	cca	gta	cct	gaa	gaa	aag	cag	ctg	cct	cca	aca	gag	590
Pro	Asp	Leu	Pro	Pro	Val	Pro	Glu	Glu	Lys	Gln	Leu	Pro	Pro	Thr	Glu	
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ttt	72021	too s	aøtti	tøct	c ti	tgtad	reces	gar	· † aaa	rat o	caat	gges	ntσ.c	ztete	aget	c 1786

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actgtaacct ccaccto	ccg gattcaagca	attcttctgc	ctcagcttcc	cgactagctg	1840
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286

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Ser	Ile	Leu	Ser	Ser	Lys	Pro	Ala	Ile	Gly	Ser	Lys	Ala	Val	Asn	Tyr	
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Ser	Ser	Thr	Gly	Ser	Ser	Lys	Ser	Phe	Cys	Ser	Cys	Val	Pro	Cys	Glu	
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Tyr	Gly	Asp	Gln	Arg	Leu	Lys	Pro	Lys	His	Thr	Lys	Leu	Phe	Val	Phe	
٠٠.	٠ ;	,	- 85	•				90					95	. ,		
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Leu	Ala	Val	Leu	Ile	Cys	Leu	Val	Thr	Ser	Ser	Phe	Ile	Val	Phe	Phe	
•••	n to	-100		r		• (	105	•				110				
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•	-115	;		5		120	, .				125	-				
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Thr	Val	A1c	Dho	400	Cl.	41.	10-	T1-	Т	ĭ	1	Tla	Th-	105	T1.	

INCOMPLETE OM- -UI-

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tta aac atc tcc aat gg	c aac tac tac ccc	att atg gtg aca cag ctg	718
Leu Asn Ile Ser Asn Gl	y Asn Tyr Tyr Pro	Ile Met Val Thr Gln Leu	
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Thr Leu Glu Val Leu Hi	s Leu Ser Leu Val	Val Gly Gln Val Ser Asn	
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Asn Leu Leu Leu His Il	e Gly Pro Leu Ala	a Ser Glu Gln Met Phe Tyr	
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Trp Leu Glu Ile Lys Va	al His His Val Leu	u Leu His Ile Gln Gly Thr	
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Leu Thr Cys Ser Tyr Le	eu Ser His Ser Glu	u Gln Leu Val Phe Gln Ser	
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Tyr Glu Tyr Val Asp C	ys Arg Gly Asn Ala	a Ser Val Pro His Gln Leu	
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Thr Pro His Pro Pro		salah kanalan dan ber	
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Met Gly Val Pro

non operation in the first process of all more than  $1,\dots,1,\dots,1,\dots$ 

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animorus — " au compane

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Thr	Ala	Leu	Glu	Ala	Gly	Ser	Trp	Arg	Trp	Gly	Ser	Leu	Leu	Phe	Ala	
5	t.;	;		•	10	•	•	•	٠	15		-	. :		20	
ctc	ttc	ctg	gct	gcg	tcc	cta	ggc	aaa	gat	gca	cca	tcc	aac	tgt	gtg	210
Leu	Phe	Leu	Ala	Ala	Ser	Leu	Gly	Lys	Asp	Ala	Pro	Ser	Asn	Cys	Val	
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gtg	tac	cca	tcc	tcc	tcc	cag	gag	agt	gaa	aac	atc	acg	gct	gca	gcc	258
Val	Tyr	Pro	Ser	Ser	Ser	Gln	Glu	Ser	Glu	Asn	Ile	Thr	Ala	Ala	Ala	
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Leu	Ala	Thr	Gly	Ala	Cys	Ile	Val	Gly	Ile	Leu	Cys	Leu	Pro	Leu	Ile	
		55					60					-65			• • • •	
ctg	ctc	ctg	gtc	tac	aag	caa	agg	cag	gca	gcc	tcc	aac	cgc	cgt	gcc	354
Leu	Leu	Leu	Val	Tyr	Lys	Gln	Arg	Gln	Ala	Ala	Ser	Asn	Arg	Arg	Ala	
	70					75					80			٠. :		
cag	gag	ctg	gtg	cgg	atg	gac	agc	aac	att	caa	ggg	att	gaa	aac	ccc	402
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				105					110					115	Appet	
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Arg	His"	Pro	Leu	Ser	Tyr	Val	Ala	Gln	Arg	·G1n	Pro	Ser	Gļu	Ser	Gly:	
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Arg His Leu Leu Ser Glu Pro Ser Thr Pro Leu Ser Pro Pro Gly Pro	
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Gly Asp Val Phe Phe Pro Ser Leu Asp Pro Val Pro Asp Ser Pro Asn	
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Phe Glu Val Ile	
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ccctgg - see on .	1556

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caccaggeca egeateacaa gaggeaacae caggagecaa e atg age teg ggg	233
Met Ser Ser Gly	
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act gaa ctg ctg tgg ccc gga gca gcg ctg ctg gtg ctg ttg ggg gtg	281
Thr Glu Leu Leu Trp Pro Gly Ala Ala Leu Leu Val Leu Leu Gly Val	
5 10 15 20	
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Ala Ala Ser Leu Cys Val Arg Cys Ser Arg Pro Gly Ala Lys Arg Ser	
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Glu Lys Ile Tyr Gln Gln Arg Ser Leu Arg Glu Asp Gln Gln Ser Phe	
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Leu	Ala	Asp	Met	Ala	Pro	Thr	Arg	Lys	Asp	Lys	Leu	Leu	Gln	Phe	Tyr		
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Gly	Ser	Arg	His	Gly	Ser	Glu	Glu	Ala	Tyr	Ile	Asp	Pro	Ile	Ala	Met		
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Glu	Tyr	Tyr	Asn	Trp	Gly	Arg	Phe	Ser	Lys	Pro	Pro	Glu	Asp	Asp	Asp	•	
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Ala	Asn	Ser	Tyr	Glu	Asn	Val	Leu	Ile	Cys	Lys	Gln	Lys	Thr	Thr	Glu		
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Thr	Gly	Ala	Gln	Gln	Glu	Gly	Ile	Gly	Gly	Leu	Cys	Arg	Gly	Asp	Leu		
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Ser	Leu	Ser	Leu	Ala	Leu	Lys	Thr	Gly	Pro	Thr	Ser	Gly	Leu	Cys	Pro		
165	.,. <b>.</b>		·. ·		170		٠.			175					180		
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Gln Arg Glu Ala Ser Pr	o Gly Pro Val	Gly Ser Pro Asp Glu	Glu Asp
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Gly Glu Pro Asp Tyr Va	l Asn Gly Glu	Val Ala Ala Thr Glu	Ala 🧎
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Lys	Asp	Cys	Lys	Lys	Ile	Ile	Cys	Asp	Lys	Tyr	Lys	Thr	Gly	Val	Ile	
3'	• 5	.• •	. 60			٠.	. •	65	:		٠,	- •	70	• .	. · · • •	
oat	- à a a	cct	oca	.tot	·aac	200	ctt	tot	att	aca	gaa	act	ctt	tac	ttt	291

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Gly	Lys	Cys	Leu	Ser	Thr	Lys	Pro	Asn	Asn	Gln	Met	Tyr	Leu	Gly	Ile	
	90					95					100		٠.	,	i •	
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٠	¹ ·.	315	, č		r,		320					325		٠,	1977 F.	
cgt	cac	tgt	gag	tct	gat	ttg	gac	tgt	gtc	tat	ggc	aca	gạt	tgt	aga	1059
Arg	His	Cys	Glu	Ser	Asp	Leu	Asp	Cys	Val	Tyr	Gly	Thr	Asp	Cys	Arg	
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to the terror and the constitution of the cons	

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عامدة بالرازية والأرازية الإ

gcct	tctc	tc	ctcgt	catc	a tc	caga	gcag	сса	gt <b>gt</b>	ccg	ggag	gcag	aa g	atg	ccc		237
		, .								٠.		·· ·		Met	Pro	٠.	
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Gln:	Lys	Ala	Ala	Leu	Val	Leu	Leu	Ser	Ala	Cys	Leu	Val	Thr	Leu	Trp		
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Arg	Thr	Va:	l Arg	Ala	Cys	Leu	Gly	Cys	Pro	Leu	Arg	Arg	Gly	Ala	Leu	٠ -	
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	. 100	) +				- 105					110	1		. ,	1		
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Asn	Leu	Ser	Met	Ala	Asp	Pro	Asn	Ile	Arg	Pḥe	Leu	Asp	Lys	Leu	Pro	
	: •			215	÷				220					225	÷.	
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Phe	Thr	Asp	Asp	Thr	His	Gly	Tyr	Ala	Val	Asn	Glu	Asp	Asp	Val	Ala
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Ara	Acn	Lau	Tvr	Sor	Ala	الم أ	٦١م	Gla	Pho	Phe	Gln	Tle	Phe	Pro	Glu

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225	٠.				230				٠,	235		· t	•		240
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			260					265					270		
Glu	Cys	Ile	Glu	His	Ile	Arg	Lys	Gln	Asn	Trp	Phe	Glu	Ala	Phe	Glu
		275					280		•	•		285		, .	÷.; «
Ile	Leu	Asp	Lys	Leu	Leu	Asp	Gly	Asp	Leu	Thr	Ser	Asp	Pro	Ser	Tyr
	290	)			•	295		•			300	<b>)</b>		, .	, .
Phe	Gln	n Asr	Val	Thr	Gly	Cys	Ser	· Asn	Туг	- Tyr	Asn	Phe	Leu	Arg	Cys
305	<b>5</b>				310	)				315	5			•	. 320
Thi	Glu	ı Pro	Glu	ı Asp	Glr	Leu	Tyr	Tyr	· Val	Lys	s Phe	e Let	. Sei	Leu	Pro
	:.	•		325	5		٠.		330	)				335	5 ( ; `
Glu	ı Val	l Ar	g Glı	n Ala	a Ile	e His	s Val	l Gly	/ Ası	n Gli	1 Tha	r Phe	e Ası	n Asp	Gly
•			340	0	4			345	5	. 1	:		35	) ·	
Th	r':11e	e Va	1 <b>G</b> 1	u Ly:	s Ty	r Lei	ı Arı	g Glu	u As	p Th	r Val	l G1:	n Se	r Va	l Lys
ı	-	35	5	· · .		٠.	36	0	· · ·			. 36	5		
Pr	o Tr	p Le	u Th	r Gl	u Il	e Me	t Ås	n Ası	n Ty	r Ly	s Va	l Le	u Il	е Ту	r Asn
•.	· '37	0 .		• • .		37	5	; <b>, .</b> E.		٠	38	0 :	·ή.	٠,٠	9.A

Gly	Gln	Leu	Asp	Ile	Ile	Val	Ala	Ala	Ala	Leu	Thr	Glu	His	Ser	Leu
385		٠.٠	. 8		390					395					400
Met	Gly	Met	Asp	Trp	Lys	Gly	Ser	Gln	Glu	Tyr	Lys	Lys	Ala	Glu	Lys
				405				,	410					415	
Lys	Val	Trp	Lys	Ile	Phe	Lys	Ser	Asp	Ser	Glu	Val	Ala	Gly	Tyr	Ile
			420					425					430		
Arg	Gln	Ala	Gly	Asp	Phe	His	Gln	Val	Ile	Ile	Arg	Gly	Gly	Gly	His
		435	-				440					445			
Ile	Leu	Pro	Tyr	Asp	Gln	Pro	Leu	Arg	Ala	Phe	Asp	Met	Ile	Asn	Arg
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Phe	Ile	Tyr	Gly	Lys	Gly	Trp	Asp	Pro	Tyr	Val	G1y				
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Met	Ser	Arg	Ala	Gln	Ile	Trp	Ala	Leu	Val	Ser	Gly	Val	Gly	Gly	Phe
1	:			. 5					10					15	,
Gly	Ala	Leu	Val	Ala	Ala	Thr	Thr	Ser	Asn	Glu	Trp	Lys	Val	Thr	Thr
			20					25					30		
Arg	Ala	Ser	Ser	Val	Ile	Thr	Ala	Thr	Trp	Val	Tyr	Gln	Gly	Leu	Trp
		35					40					45			
Met	Asn	Cys	Ala	Gly	Asn	Ala	Leu	Gly	Ser	Phe	His	Cys	Arg	Pro	His

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	50	-	••		• 0	55					60	-			٠
Phe '	Thr	Ile	Phe	Lys	Val	Ala	Gly	Tyr	Ile	Gln	Ala	Cys	Arg	Gly	Leu
65	,				70	•		٠		75	•	• •		~1	80
Met	Ile	Ala	Ala	Val	Ser	Leu	Gly	Phe	Phe	Gly	Ser	Ile	Phe	Ala	Leu
		- , •		85	.*	• •	•		90				. •	95	·
Phe	Gly	Met	Lys	Cys	Thr	Lys	Val	Gly	Gly	Ser	Asp	Lys	Ala	Lys	Ala
			100					105	٠				110		\$
Lys	Ile	Ala	Cys	Leu	Ala	Gly	Ile	Val	Phe	Ile	Leu	Ser	Gly	Leu	Cys
		115	•			٠	120		• .		-	125	•	•	
Ser	Met	Thr	Gly	Cys	Ser	Leu	Tyr	Ala	Asn	Lys	Ile	Thr	Thr	Glu	Phe
	130					135				•	140				
Phe	Asp	Pro	Leu	Phe	Val	Glu	Gln	Lys	Tyr	Glu	Leu	Gly	Ala	Ala	Leu
145					150					155					160
Phe	Ile	Gly	Trp	Ala	Gly	Ala	Ser	Leu	Cys	Ile	Ile	Gly	Gly	Val <sup>-</sup>	Ile
				165					170					175	
Phe	Cys	Phe	Ser	Ile	Ser	Asp	Asn	Asn	Lys	Thr	Pro	Arg	Tyr	Thr	Tyr
			180	1				185					190		
Asn	Gly	Ala	Thr	Ser	Val	Met	Ser	Ser	Arg	Thr	Lys	Tyr	His	Gly	Gly
		195					200		·			205		•	
Glu															Ala:
	210	. 1		•		215	•			••	220		1	×	Pt. + 1
Tyr													٠		
225	~ 4		. • •	•	5.		•	. •	•	• •	•			. 4.	

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<212	2> <sub>.</sub> PI	RT .													
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Met	Gly	Ile	Gln	Thr	Ser	Pro	Val	Leu	Leu	Ala	Ser	Leu	Gly	Val	Gly
1				5					10					15	
Leu	Val	Thr	Leu	Leu	Gly	Leu	Ala	Val	Gly	Ser	Tyr	Leu	Val	Arg	Arg
			20					25					30		•
Ser	Arg	Arg	Pro	Gln	Val	Thr	Leu	Leu	Asp	Pro	Asn	Glu	Lys	Tyr	Leu
		35					40					45			
Leu	Arg	Leu	Leu	Asp	Lys	Thr	Thr	Val	Ser	His	Asn	Thr	Lys	Arg	Phe
	50					55					60				
Arg	Phe	Ala	Leu	Pro	Thr	Ala	His	His	Thr	Leu	Gly	Leu	Pro	Val	Gly
65					70					75					80
Lys	His	Ile	Tyr	Leu	Ser	Thr	Arg	Ile	Asp	Gly	Ser	Leu	Val	Ile	Arg
ı	-•	•		85					90			,		95	
Pro	Tyr	Thr	Pro	Val	Thr	Ser	Asp	Glu	Asp	Gln	Gly	Tyr	Val	Asp	Leu
			100					105					110		
Val	Ile	Lys	Val	Tyr	Leu	Lys	Gly	Val	His	Pro	Lys	Phe	Pro	Glu	Gly
		115					120					125			
Gly	Lys	Met	Ser	Gln	Tyr	Leu	Asp	Ser	Leu	Lys	Val	Gly	Asp	Val	Val
	130					135					140			· ·	
Glu	Phe	Arg	Gly	Pro	Ser	Gly	Leu	Leu	Thr	Tyr	Thr	Gly	Lys	Gly	His
145					150					155	ŧ				160
Phe	Asn	Ile	Gln	Pro	Asn	Lys	Lys	Ser	Pro	Pro	Glu	Pro	Arg	Val	Ala

BNCUCIU--MU UTTSEEUTS I

				165					170					175	• :	
Lys	Lys	Leu	Gly	Met	Ile	Ala	Gly	Gly	Thr	Gly	Ile	Thr	Pro	Met	Leu	
			180					185					190	•	Sec.	-
G1n	Leu	Ile	Arg	Ala	Ile	Leu	Lys	Val	Pro	Glu	Asp	Pro	Thr	Gln	Cys	
	٠ ,	195			٠.		200					205		.: •	,	
Phe	Leu	Leu	Phe	Ala	Asn	Gln	Thr	Glu	Lys	Asp	Ile	Ile	Leu	Arg	Glu	
	210					215	•				220				,	
Asp	Leu	Glu	Glu	Leu	Gln	Ala	Arg	Tyr	Pro	Asn	Arg	Phe	Lys	Leu	Trp	
225				•	230	•	ė			235					240	
Phe	Thr	Leu	Asp	His	Pro	Pro	Lys	Asp	Trp	Ala	Tyr	Ser	Lys	Gly	Phe	
				245					250				٠.	255		
Val	Thr	Ala	Asp	Met	Ile	Arg	Glu	His	Leu	Pro	Ala	Pro	Gly	Asp	Asp	
			260	)				265		٠			270		3	
Val	Leu	Val	Leu	Leu	Cys	Gly	Pro	Pro	Pro	Met	Val	G1n	Leu	Ala	Cys	
		275	<b>;</b> '				280	ı				285				
His	Pro	Asr	ı Let	ı Asp	Lys	Leu	Gly	Tyr	Ser	Gln	Lys	Met	. Arg	Phe	Thr	
	290	)			,	295					300			,		٠.
Tyı	•															
30	5	÷					•	*	•	,	•					12
<2	10> '	94	٠				ċ			:		,	•	. :	• "	•
<2	11>	227												١		
<2	12>	PRT	••			.*			•			•	;	٠	·, ·••	7
			_	iens											7.2	
<4	00>	94	÷ .,	:	'	: :	:			• •		. : •	1 -5	' . : <b>'</b>	•	, ;

Ме	t Gl	y Tr	p Th	r Mei	t Arg	, Lei	ı Va	l Thi	- Ala	a Ala	Lei	ı Lei	u Le	u Gl	y Leu
,	l ,	•	•	8	5		. •		10	)				15	5 .
Me	t Me	t Va	l Va	l Thr	Gly	Asp	Glu	ı Asp	Glu	ı Asr	Sei	Pro	Cy:	s Ala	a His
			20	)				25	;				30	) .	
Glu	ı Ala	a Lei	ı Lei	ı Asp	Glu	Λsp	Thr	Leu	Phe	Cys	Glr	Gly	/ Lei	ı Glu	ı Val
		38	5				40	)				45	5		
Phe	: Туг	Pro	o Glu	ı Leu	Gly	Asn	Ile	Gly	Cys	Lys	Val	Val	Pro	Asp	Cys
	50	)				55	ı				60	)			,
Asn	Asn	Туг	Arg	Gln	Lys	Ile	Thr	Ser	Trp	Met	Glu	Pro	Ile	· Val	Lys
65					70					75					80
Phe	Pro	Gly	Ala	Val	Asp	Gly	Ala	Thr	Tyr	Ile	Leu	Val	Met	Val	Asp
	• • •			85		•			90					95	
Pro	Λsp	Ala	Pro	Ser	Arg	Ala	Glu	Pro	Arg	Gln	Arg	Phe	Trp	Arg	His
			100					105					110		
Trp	Leu	Val	Thr	Asp	Ile	Lys	Gly	Ala	Asp	Leu	Lys	Lys	Gly	Lys	Ile
	:	115					120					125		٠.	. · · ·
Gln	Gly	Gln	Glu	Leu	Ser	Ala	Tyr	Gln	Ala	Pro	Ser	Pro	Pro	Ala	His
	130					135					140				
Ser	Gly	Phe	His	Arg	Tyr	Gln	Phe	Phe	Val	Tyr	Leu	Gin	Glu	Gly	Ĺys
145					150					155				;	160
Val	Ile	Ser	Leu	Leu	Pro	Lys	Glu	Asn	Lys	Thr	Arg	Gly	Ser	Trp	Lys -
	•	• •		165				•	170			•		175	
Met	Asp	Arg	Phe	Leu	Asn	Arg	Phe	His	Leu	Gly	Glu	Pro	Glų	Ala	Ser
	( <del>-</del>	:	180		,			185		,			190	٠٠,	
Thr	Gln	Phe	Met	Thr	Gln .	Asn	Tyr	Gln	Asp	Ser	Pro	Thr	Leu	Gln	Ala

195 200 205 Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn Gln Ala Glu Ile 210 215 220 Ala Ala Cys **225** <210> 95 <211> 441 <212> PRT <213> Homo sapiens <400> 95 Met Ala Ile His Lys Ala Leu Val Met Cys Leu Gly Leu Pro Leu Phe . 15 1 10 5 Leu Phe Pro Gly Ala Trp Ala Gln Gly His Val Pro Pro Gly Cys Ser 30 20 25 Gln Gly Leu Asn Pro Leu Tyr Tyr Asn Leu Cys Asp Arg Ser Gly Ala 40 45 Trp Gly Ile Val Leu Glu Ala Val Ala Gly Ala Gly Ile Val Thr Thr 60 50 55 Phc Val Leu Thr Ile Ile Leu Val Ala Ser Leu Pro Phe Val Gln Asp 65 70 75 75 80 Thr Lys Lys Arg Ser Leu Leu Gly Thr Gln Val Phe Phe Leu Leu Gly 85 90 95 Thr Leu Gly Leu Phe Cys Leu Val Phe Ala Cys Val Val Lys Pro Asp ... 100 me to the 105 me to the 110 me and the

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Phe	Ser	Thi	Cys	Ala	Ser	Arg	Arg	Phe	Leu	Phe	Gly	Val	Leu	Phe	Ala
	• • •	115	5		•	٠.	120	1				125			
He	Cys	Phe	e Ser	Cys	Leu	Ala	Ala	His	Val	Phe	Ala	Leu	Asn	Phe	Leu
	130					135	ı				140		,		
Ala	Arg	Lys	. Asn	His	Gly	Pro	Arg	Gly	Trp	Val	Ile	Phe	Thr	Val	Ala
145					150					155					160
Leu	Leu	Leu	Thr	Leu	Val	Glu	Val	Ile	Ile	Asn	Thr	Glu	Trp	Leu	Ile
				165					170					175	
Ile	Thr	Leu	Val	Arg	Gly	Ser	Gly	Glu	Gly	Gly	Pro	G1n	Gly	Asn	Ser
			180					185					190		
Ser	Ala	Gly	Trp	Ala	Val	Ala	Ser	Pro	Cys	۸la	Ile	Ala	Asn	Met	Asp
		195					200					205		-	
Phe	Val	Met	۸la	Leu	Ile	Tyr	Val	Met	Leu	Leu	Leu	Leu	Gly	Ala	Phe
	210					215					220				
Leu	Gly	Ala	Trp	Pro	Ala	Leu	Cys	Gly	Arg	Tyr	Lys	Arg	Trp	Arg	Lys
225					230					235	٠			,	240
His	Gly	Val	Phe	Val	Leu	Leu	Thr	Thr	Ala	Thr	Ser	Val	Ala	Ile	Trp
				245					250					255	
Val	Val	Trp	Ile	Val	Met	Tyr	Thr	Tyr	Gly	Asn	Lys	Gln	His	Asn	Ser
			260					265						:	
Pro	Thr	Trp	Asp	Asp	Pro	Thr	Leu	Ala	lle	Ala	Leu	Ala	Ala	Asn	Ala
		275					280					285			٠.
															Thr
	·290		· . · ·	-		295	. • •				300	•		A.	:
Lvs	Ser	Ser	Pro	Glu	Gln	Ser	Tvr	Gln	Glv	Aen	Mot	Tvr	Pro	Thr	Ara

305	1 · ·			٠.,	310	•				315			•		320′	
Gly	Val	Gly	Tyr	Glu	Thr	Ile	Leu	Lys	Glu	Gln	Lys	Gly	Gln	Ser	Met	
	;	:		325					330		,		9.0	335	.•.	
Phe	Val	Glu	Asn	Lys	Ala	Phe	Ser	Met	Asp	Glu	Pro	Val	Ala	Ala	Lys	
	:.		340	, 8	: •			345					350		٠.	
Arg	Pro	Val	Ser	Pro	Tyr	Ser	Gly	Tyr	Asn	Gly	Gln	Leu	Leu	Thr	Ser	
		355					360					365				
Val	Tyr	Gln	Pro	Thr	Glu	Met	Ala	Leu	Met	His	Lys	Val	Pro	Ser	Glu	
	370		. *			375					380				,	
Gly	Ala	Tyr	Asp	Ile	Ile	Leu	Pro	Arg	Ala	Thr	Ala	Asn	Ser	Gln	Val	
385	٠.	-		•	390					395					400	
Met	Gly	Ser	Ala	Asn	Ser	Thr	Leu	Arg	Ala	Glu	Asp	Met	Tyr	Ser	Ala	
	٠.	÷		405					410					415		
Gln	Ser	His	Gln	Ala	Ala	Thr	Pro	Pro	Lys	Asp	Gly	Lys	Asn	Ser	Gln	
•	. ;	•	420					425			•		430		٠٠.	
Val	Phe	Arg	Asn	Pro	Tyr	Val	Trp	Λsp			-					
	1.1	435				•	440							•		
							,									
<21	0> 9	6								. ,				, .	`,	
<21	1> 2	65	٠.													
<21	2> P	RT ·					,				•		. ,		. ,	
<21	3> H	omo	sapi	ens:										٠.,		
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Met	Ala	Ala	Ala	Val	Pro	Lys	Arg	Met	Arg	Gly	Pro	Ala	Gln	Ala	Lys	
								,	.10	. , .				15		

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Leu	Leu	Pro	Gly	Ser	Ala	Ile	Gln	Ala	Leu	Val	Gly	Leu	Ala	Arg	Pro	
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Leu	Val	Leu	Ala	Leu	Leu	Leu	Val	Ser	Ala	Ala	Leu	Ser	Ser	Val	Val	
	٠.	35				-	40					45				
Ser	Arg	Thr	Asp	Ser	Pro	Ser	Pro	Thr	Val	Leu	Asn	Ser	His	Ile	Ser	
	50					55					60					
Thr	Pro	Asn	Val	Asn	Ala	Leu	Thr	His	Glu	Asn	Gln	Thr	Lys	Pro	Ser	
65					70					75					80	
Ile	Ser	Gln	Ile	Ser	Thr	Thr	Leu	Pro	Pro	Thr	Thr	Ser	Thr	Lys	Lys	
				85					90					95		
Ser	Gly	Gly	Λla	Ser	Val	Val	Pro	His	Pro	Ser	Pro	Thr	Pro	Leu	Ser	
			100					105					110			
Gln	Glu	Glu	Ala	Asp	Asn	Asn	Glu	Asp	Pro	Ser	He	Glu	Glu	Glu	Asp	
		115					120					125				
Leu	Leu	Met	Leu	Asn	Ser	Ser	Pro	Ser	Thr	Ala	Lys	Asp	Thr	Leu	Asp	
	130					135					140		:	1		
Asn	Gly	Asp	Tyr	Gly	Glu	Pro	Asp	Tyr	Asp	Trp	Thr	Thr	Gly	Pro	Arg	
145					150					155					160	
Asp	Asp	Asp	Glu	Ser	Asp	Asp	Thr	Leu	Glu	Glu	Asn	Arg	Gly	Tyr	Met	
				165					170				•	175	÷ ••	
Glu	Ile	Glu	Gln	Ser	Val	Lys	Ser	Phe	Lys	Met	Pro	Ser	Ser	Asn	Ile	
	• ; •		180					185					190	1.		1
Glu	Glu	Glu	Asp	Ser	His	Phe	Phe	Phe	llis	Leu	Ile	lle	Phe	Ala	Phe	
	<b>:</b>	195	. • •	,			200			,	•	205		. :	• 6	
Cys	Пe	Ala	Val	Val	Tyr	He	Thr	Tvr	His	Asn	Lvs	Arg	Lvs	lle	Phe	

210				215	٠.		. '		220		4	.*•	٠.٠	•
Leu Leu Val	Gln	Ser	Arg	Lys	Trp	Arg	Asp	Gly	Leu	Cys	Ser	Lys	Thr	
<b>225</b>		1 .	230	• •	•			235	•		•	•. •	240	
Val Glu Tyr	His	Arg	Leu	Asp	Gln	Asn	Val	Asn	Glu	Ala	Met	Pro	Ser	
; **	. ;	245		•	9 .	,.	250	• • •		•**.		255		•
Leu Lys Ile	Thr	Asn	Λsp	Tyr	Ile	Phe								
• .	260			٠		265	•				•	÷		
	•													
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Met Leu Gly	/ Leu	Leu	Val	Ala	Leu	Leu	Ala	Leu	Gly	Leu	Ala	Val	Phe	
1		5					10					15		• '
Ala Leu Le	ı Asp	Val	Trp	Tyr	Leu	Val	Arg	Leu	Pro	Cys	Ala	Val	Leu	
Jones.	20	,				25			٠.	- : * *	30		*	
Arg Ala Ar	g Leu	Leu	Gln	Pro	Arg	Val	Arg	Asp	Leu	Leu	Ala	Glu	Gln	
: 38	5 ·				40			•		45			.:	
Arg Phe Pro	o Gly	Arg	Val	Leu	Pro	Ser	Asp	Leu	Asp	Leu	Leu	Leu	His	
· 50 · · ·			. ,	55					60		. • •		1.	
Met Asn As	n Ala	Arg	Tyr	Leu	Arg	Glu	Λla	Asp	Phe	Λla	Arg	Val	Ala	
65		٠. ٠	·70		* *	•		<b>7</b> 5	,		ı	• 1	80	
His Leu Th	r Arg	Cys	Gly	Val	Leu	Gly	Ala	Leu	Arg	Glu	Leu	Arg	Ala	
Sant 1		85					90	: . :	٠,		. 44 -	.95	41.	.`

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His	Thr	Val	Leu	Ala	Ala	Ser	Cys	Ala	Arg	His	Arg	Arg	Ser	Leu	ı Arg	
	• .		100		•			105		٠.			110	)	• •	
Leu	Leu	Glu	Pro	Phe	Glu	Val	Arg	Thr	Arg	Leu	Leu	Gly	Trp	Asp	Asp	•
	4.	115					120	)				125				
Arg	Ala	Phe	Tyr	Leu	Glu	Ala	Arg	Phe	Val	Ser	Leu	Arg	Λsp	Gly	Phe	
	130					135					140					
Val	Cys	Ala	Leu	Leu	Arg	Phe	Arg	Gln	His	Leu	Leu	Gly	Thr	Ser	Pro	
145					150					155					160	
Glu	Λrg	Val	Val	Gln	His	Leu	Cys	Gln	Arg	Arg	Val	Glu	Pro	Pro		
				165					170					175		
Leu	Pro	Ala	Asp	Leu	Gln	His	Trp	lle	Ser	Tyr	Asn	Glu	Ala			
			180				-	185		·			190			
Gln	Leu	Leu	Arg	Met	Glu	Ser	Gly		Ser	Asp	Vai	Thr		Asn	Gln	
		195	•				200					205	.,, 0	пор	01	
<210	>. 98	<b>.</b>														
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<212																
<213			anio	ne												
														•		
															Leu	
															4 -	-
Ala I																
	٠.,	*	20,	٠. ,	,			25	٠.				30	٠,	٠,	٠.
Arg A	Ala.∣	Leu (	Glu '	Trp	Phe	Ser.	Ala	Val	Val	Asn	Ile	Glu	Tyr	Val	Asp	

	la 11	<sup>-</sup> 35		٠,		ì	40		•		•	45				٠.
Pro	Gln	Thr	Asn	Leu	Thr	Val	Trp	Ser	Val	Ser	Glu	Ser	Gly	Arg	Phe	
	50	×		٠.		55			٠.		60	•	•			
Gly	Asp	Ser	Ser	Pro	Lys	G1u	Gly	Ala	His	Gly	Leu	Val	Gly	Val	Pro	
65	1.1			. •	70		. •			75					80	
Trp	Ala	Pro	Gly	Gly	Λsp	Leu	Glu	Gly	Cys	Ala	Pro	Asp	Thr	Arg	Phe	
				85					90					95	i	
Phe	Val	Pro	Glu	Pro	Gly	Gly	Arg	Gly	Ala	Ala	Pro	Trp	Val	Ala	Leu	
			100					105					110	:		·
Val	Ala	Arg	Gly	Gly	Cys	Thr	Phe	Lys	Asp	Lys	Val	Leu	Val	Ala	Ala	
		115					120					125				
Arg	Arg	Asn	Λla	Ser	Ala	Val	Val	Leu	Tyr	Asn	Glu	Glu	Arg	Tyr	Gly	
•	130					135					140			,		
Asn	lle	Thr	Leu	Pro	Met	Ser	His	Ala	Gly	Thr	Gly	Asn	Ile	Val	Val	
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His Leu Leu Glu Ala Glu Trp Gly Ala	Asp Gli 100 Pro Ari	a Glu 5 n Gln g Asn	Ala Ser Gln	Arg Asp 120 Leu	Val 105 Pro	90 Leu Ala Arg	Ala Leu	Gln Gly Leu	Leu Leu 125	Leu 110 Asp	95 Arg  Asp	Gln Val Asp

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Pro <sup>·</sup>	Tyr	Ile	Glu	Ala	Gly	Lys	He	Gln	Lys	Gly	Arg	Glu	Leu	Ser	Leu	,	
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Val	Gly	Pro	Phe	Pro	Gly	Leu	Asn	Met	Lys	Ser	Tyr	Ala	Gly	Phe	Leu		
	: .	¹ 65		٠.	•	1	70	1	*		. :	75	. 1	ė	•. •	. •	
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Thr	Val	Asn	Lys	Thr	Tyr	Asn	Ser	۸sn	Leu	Phe	Phe	Trp	Phe	Phe	Pro	•	
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Gly	Pro	Gly	Gly	Ser	Ser	Met	Phe	Gly	Leu	Phe	Val	Glu	llis	Gly	Pro		
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Tyr	Val	Val	Thr												Trp	•	
	¥ .	•••	130	•	•			135	•		•	•	140	• •			
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Thr	Thr	Thr	Leu	Ser	Met	Leu	Tyr	Ile	Asp	Asn	Pro	Val	Gly	Thr	Gly	•	
	1 .	145	, 1	•	: .	: •	150	'		•	٠	155	• •		- * *	· -	
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Phe	Ser														Asp		
	160														() - 3		
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Val	Ala	۸rg	Asp	Leu	Tyr	Ser	Ala	Leu	He	Gln	Pho	Phe	Gln	lle	Phe	.;	

175	5				180	)	÷			185	5				190		
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Pro	Glu	т Ту	r Lys	Asr	Asn	Asp	Phe	Tyr	· Val	Thr	Gly	/ Glu	Ser	Туг	Ala		
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Tyr	Ser	Asp	Pro	Glu	Ser	Ile	Ile	Gly	Gly	Tyr	Ala	Glu	Phe	Leu	Tyr		
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Cys	His	G1u	Cys	Ile	Glu	His	lle	Arg	Lys	Gln	Asn	Trp	Phe	Glu	Ala		
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Phe	Ģlų	Ile	Leu	Asp	Lys	Leu	Leu	Asp	Gly	Asp	Leu	Thr	Ser	Asp	Pro		
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Ser	Tyr	Phe	Gln	Asn	Val	Thr	Gly	Cys	Ser	Λsn	Tyr	Tyr	Asn	Phe	Leu		
	100	305	2.4	; <b>.</b>	; .		310	٠,.	٠٠.	ا د ز	٠,,٠	315	1.1		*		

				4		-n+	000	ott	tac	tat	ata	222	t t t	ttσ	tca	1069
			gaa													1000
Arg	Cys	Thr	Glu	Pro	Glu	Asp	Gln	Leu	Tyr	Tyr						•
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Tyr	Asn	Gly	Gln	Leu	Asp	Ile	Ile	Val	Ala	Ala	Ala	Leu	Inr	GIU		
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Gly Gly Phe Gly Ala Leu Val Ala Ala Thr Thr Scr Asn Glu Trp Lys	

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Gly	Leu	Cys	Ser	Met	Thr	Gly	Cys	Ser	Leu	Tyr	Ala	Asn	Lys	Ile	Thr	•	
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Thr	Glu	Phe	Phe	Aśp	Pro	Leu	Phe	Val	Glu	Gln	Lys	Tyr	Glu	Leu	Gly	;	
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Leu	Leu	Asp	Pro	Asn	Glu	Lys	Tyr	Leu	Leu	Arg	Leu	Leu	Asp	Lys	Thr		
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Thr	Val	Ser	His	Asn	Thr	Lys	Arg	Phe	Arg	Phe	Ala	Leu	Pro	Thr	۸ľa		
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His	His	Thr	Leu	Gly	Leu	Pro	Val	Gly	Lys	His	Ile	Tyr	Leu	Ser	Thr		
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gat	gag	gat	caa	ggc	tat	gtg	gat	ctt	gtc	atc	aag	gtc	tac	ctg	aag ·		390

Asp Glu Ası	Gln Gly T	r Val Asp I	Leu Val Ile	Lys Val Tyr	Leu Lys
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Gly Val His	Pro Lys P	ne Pro Glu (	Gly Gly Lys	s Met Ser Gln	Tyr Leu
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185	- 、 ※	i'80	••	195	A Production
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200	2	05	. 210	) <u> </u>	215
aca gaa aa	g gat atc a	tc ttg cgg	gag gac tta	a gag gaa ctg	cag gcc 726
Thr Glu Ly	s Asp Ile I	le Leu Arg (	Glu Asp Leu	a Glu Glu Leu	Gln Ala
. ••	220		225		230
cgc tat cc	aat cgc t	it aag ctc	tgg ttc act	t cig gat cat	ccc cca 774
Arg Tyr Pro	Asn Arg P	ne Lys Leu '	Trp Phe Thi	r Leu Asp His	Pro Pro

• • • • •	235	249		245	*
aaa gat tgg	gcc tac agc	aag ggc ttt	gtg act gcc	gac atg atc	c'gg 822
Lys Asp Trp	Ala Tyr Ser	Lys Gly Phe	Val Thr Ala	Asp Met Ile	Arg
250	. *	255	•	260 ·	.:
gaa cac ctg	ccc gct cca	ggg gat gat	gtg ctg gta	ctg ctt tgt	ggg 870
Glu His Leu	Pro Ala Pro	Gly Asp Asp	Val Leu Val	Leu Leu Cys	Gly
265	•	270	275	•	
cca ccc cca	atg gtg cag	ctg gcc tgc	cat ccc aac	ttg gac aaa	ctg 918
Pro Pro Pro	Met Val Gln	Leu Ala Cys	His Pro Asn	Leu Asp Lys	Leu
280	285		290		295
ggc tac tca	caa aag atg	cga ttc acc	tac tg agca	tcctcc agctt	ccctg 970
Gly Tyr Ser	Gln Lys Met	Arg Phe Thr	Tyr	. •	
	300		305		
gtgctgttcg	ctgcagttgt t	cccatcag ta	ctcaagca cta	taagcct taga	ttcctt 1030
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ctg	cctt	tcc	ttct	ccct	gt g	ctta	acca	g ag	gtgc	cc a	tg g	gt t	gg a	ica a	tg			113
										М	et G	ly T	rp T	hr M	let			
											1				- 5			
agg	ctg	gtc	aca	gca	gca	ctg	tta	ctg	ggt	ctc	atg	atg	gtg	gtc	act	:		161
Arg	Leu	Val	Thr	Ala	Ala	Leu	Leu	Leu	Gly	Leu	Met	Met	Val	Val	Thr	•		
				10		•			15					20				
gga	gac	gag	gat	gag	aac-	agc	ccg	tgt	gcc	cat	gag	gcc	ctc	ttg	gac	:		209
Gly	Asp,	Glu	Asp	Glu	Asn	Ser	Pro	Cys	Ala	His	Glu	Ala	Leu	Leu	Asp			
	•		25					30				٠.	35					
gag	gac	acc	ctc	ttt	tgc	cag	ggc	ctt	gaa	gtt	ttc	tac	cca	gag	ttg	•		257
Glu	Asp	Thr	Leu	Phe	Cys	Gln	Gly	Leu	Glu	Val	Phe	Tyr	Pro	Glu	Leu			
	• • •	40					45	•		•		50			•	• .		
ggg	aac,	att	ggc	tgc	aag	gtt	gtt	cct	gat	tgt	aac	aac	tac	aga	cag		. ;	305
Gly	Asn	Ile	G1 y	Cys	Lys	Val	Val	Pro	Asp	Cys	Asn	Λsn	Tyr	Arg	Gln			
	<b>55</b> .					60	-	٠٠.	-		65	,•÷		•• •				
aag	atc	acc	tcc-	tgg	atg	gag	ccg	ata	gtc	aag	ttc	ccg	ggg	gcc	gtg		;	353

Lys	Ile	Thr	Ser	Trp	Met	Glu	Pro	Ile	Val	Lys	Phe	Pro	Gly	Ala	Val	•	
70					75					80					·· 85	•	
gac	ggc	gca	acc	tat	atc	ctg	gtg	atg	gtg	gat	cca	gat	gcc	cct	agc		401
Asp	Gly	Ala	Thr.	Tyr	Ile	Leu	Val	Met	Val	Asp	Pro	Asp	Ala	Pro	Ser		
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aga	gca	gaa	ccc	aga	cag	aga	tic	tgg	aga	cat	tgg	ctg	gta	aca	gat	•	449
Arg	Λla	Glu	Pro	Arg	Gln	Arg	Phe	Trp	Arg	His	Trp	Leu	Val	Thr	Asp		
			105					110					115		i.	•	
atc	aag	ģgc	gcc	gac	ctg	aag	aaa	ggg	aag	att	cag	ggc	cag	gag	tta	•00	497
Ile	Lys	Gly	Ala	Asp	Leu	Lys	Lys	Gly	Lys	Ile	Gln	Gly	Gln	Glu	Leu		
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Ser	Ala	Tyr	Gln	Ala	Pro	Ser	Pro	Pro	Ala	His	Ser	Gly	Phe	His	Arg		
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Tyr	Gln	Phe	Phe	Val	Tyr	Leu	Gln	Glu	Gly	Lys	Val	Ile	Ser	Leu	Leu	-	
150	¥	1.	٠.		155	• •			٠.	160		**		1,	165	•••	
ccc	aag	gaa	aac	aaa	act	cga	ggc	tct	tgg	aaa	atg	gac	aga	ttt	ctg		641
Pro	Lys	Glu	Asn	Lys	Thr	Arg	Gly	Ser	Trp	Lys	Meț	Asp	Arg	Phe	Leu		
	;			170	1		٠.		175	•		•••	•	180	ζ, .	•	
aac	cgt	ttc	cac	ctg	ggc	gaa	cct	gaa	gca	agc	acc	cag	ttc	atg	acc		689
Asn	Arg	Phe	His	Leu	Gly	Glu	Pro	Glu	Ala	Ser	Thr	Gln	Phe	Met	Thr		
	• • •		185	٠		٠٠.	•	190			٠		195	٠,	• .		
cag	aac	tac	cag	gac	tca	cca	acc	ctc	cag	gct	ccc	aga	gaa	agg	gcc		737
Gln	Asn	Tyr	Gln	Asp	Ser	Pro	Thr	Leu	Gln	Ala	Pro	Arg	Glu	Arg	Ala	٠,	

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Ser Glu Pro Lys His Lys	Asn Glm Ala Glu Ile	Ala Ala Cys	
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gagcctggcc tgggagccag g	atg gcc atc cac aaa	gcc ttg gtg atg tgc	171
	Met Ala Ile His Lys	Ala Leu Val Met Cys	
F. F. H. A.	.1 5	. 10	
ctg gga ctg cct ctc ttc	ctg ttc cca ggg gcc	tgg gcc cag ggc cat	219
Leu Gly Leu Pro Leu Phe	Leu Phe Pro Gly Ala	Trp Ala Gln Gly His	
	20 ,	25	
gtc cca ccc ggc tgc agc	caa ggc ctc aac ccc	ctg tac tac aac ctg	267
Val Pro Pro Gly Cys Ser	Gln Gly Leu Asn Pro	Leu Tyr Tyr Asn Leu	

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tgt	gac	cgc	tct	ggg	gcg	tgg	ggc	atc	gtc	ctg	gag	gcc	gtg	gct	ggg		315
Cys	Asp	Arg	Ser	Gly	Ala	Trp	Gly	Ile	Val	Leu	Glu	Ala	Val	Ala	Gly		
		45			٠		50					55			••••		
gcg	ggc	att	gtc	acc	acg	ttt	gtg	ctc	acc	atc	atc	ctg	gtg	gcc	agc	•	363
Ala	Gly	Ile	Val	Thr	Thr	Phe	Val	Leu	Thr	Ile	Ile	Leu	Val	Ala	Ser		
	60					65					70						
ctc	ccc	ttt	gtg	cag	gac	acc	aag	aaa	cgg	agc	ctg	ctg	ggg	acc	cag		411
Leu	Pro	Phe	Val	Gln	Asp	Thr	Lys	Lys	۸rg	Ser	Leu	Leu	Gly	Thr	Gln	1	
75					80					85					90		
gta	ttc	ttc	ctt	ctg	ggg	acc	ctg	ggc	ctc	ttc	tgc	ctc	gtg	ttt	gcc		459
Va]	Phe	Phe	Leu	Leu	Gly	Thr	Leu	Gly	Leu	Phe	Cys	Leu	Val	Phe	Ala		
				95					100					105	•		
tgt	gtg	gtg	aag	ccc	gac	ttc	tcc	acc	tgt	gcc	tct	cgg	cgc	ttc	ctc		507
Cys	Val	Val	l.ys	Pro	Asp	Phe	Ser	Thr	Cys	Ala	Ser	Arg	Arg	Phe	Leu		
		•,	110	•		٠.		115					120		-		
tti	ggg	gtt	ctg	ttc	gcc	atc	tgc	ttc	tct	tgt	ctg	gcg	gct	cac	gtc	**	555
Phe	Gly	Val	Leu	Phe	Ala	Ile	Cys	Phe	Ser	Cys	Leu	Ala	Ala	His	Val		
		125					130					135	•				
ιtι	gcc	ctc	aac	ttc	ctg	gcc	cgg	aag	aac	cac	ggg	ccc	cgg	ggo	tgg		603
Phe	Ala	Leu	Asn	Phe	Leu	Ala	Arg	Lys	Asn	His	Gly	Pro	Arg	Gly	Trp		
	-140	-••	٠ ـ .	٠.		145	•	•		٠.	150		•		( a 1.		
															atc		651
Val	lle	Phe	Thr	· Val	Ala	Leu	Leu	Leu	Thr	Leu	Val	Glu	ı Val	Ile	lle	•	
					1.00		_			166					. 170	. •	

BNSDDCID: <WO 0112880A2 I

Zaktovskih i nam i nastv

aat	aca	gag	gtgg	ctg	atc	ato	acc	ctg	gtt	cgg	ggc	agt	gg	c gag	g ggc	699
Asn	Thr	Glu	Trp	Leu	Ile	Ile	Thr	Leu	Val	Arg	Gļy	Ser	Gl	y Glu	Gly	
				175	3		•		180					185	5	
ggc	cct	. cag	ggo	aac	agc	agc	gca	ggc	tgg	gcc	gtg	gcc	tco	ccc	tgt ,	747
G1 y	Pro	Gln	Gly	Asn	Ser	Ser	Ala	Gly	Trp	Ala	Val	Ala	Sei	Pro	Cys	
			190	+				195					200	)		
gcc	atc	gcc	aac	atg	gac	ttt	gtc	atg	gca	ctc	atc	tac	gto	atg	ctg	795
Ala	Ile	Ala	Asn	Met	Asp	Phe	Val	Met	Ala	Leu	Ile	Tyr	Val	Met	Leu	
		205					210					215				
ctg	ctg	ctg	ggt	gcc	ttc	ctg	ggg	gcc	tgg	ccc	gcc	ctg	tgt	ggc	cgc	843
Leu	Leu	Leu	Gly	Ala	Phe	Leu	Gly	Ala	Trp	Pro	Ala	Leu	Cys	Gly	Arg	
	220					225					230				••	
tac	aag	cgc	tgg	cgt	aag	cat	ggg	gtc	ttt	gtg	ctc	ctc	acc	aca	gcc	891
Tyr	Lys	Arg	Trp	Arg	Lys	His	Gly	Val	Phe	Val	Leu	Leu	Thr	Thr	Ala	
235					240					245					250	
acc	tcc	gtt	gcc	ata	tgg	gtg	gtg	tgg	atc	gtc	atg	tat	act	tac	ggc	939
Thr	Ser	Val	Ala	He	Trp	Val	Val	Trp	Ile	Val	Met	Tyr	Thr	Tyr	Gly	
	٠.			255					260					265		
aac	aag	cag	cac	aac	agt	ccc	acc	tgg	gat	gac	ccc	acg	ctg	gcc	atc	987
Asn	Lys	Gln	His	Asn	Ser	Pro	Thr	Trp	Asp	Asp	Pro	Thr	Leu	Ala	Ile	
			270				٠	275					280			
gcc	ctc	gcc	gcc	aat	gcc	tgg	gcc	ttc	gtc	ctc	ttc	tac	gtc	atc	ccc	1035
Ala	Leu	Ala	Ala	Asn	Ala	Trp	Ala	Phe	Val	Leu	Phe	Tyr	Val	Ile	Pro	
		285	•	•	*	-	290					295		٠.٠	· ·	
gag	gtc	tcc	cag	gtg	acc	aag	tcc	agc	сса	gag	caa	agc	tac	cag	ggg	1083

Glu	Val	Ser	Gln	Val	Thr	Lys	Ser	Ser	Pro	Glu	Gln	Ser	Tyr	Gln	Gly		
	300					305	1 3	, ,4	- •	. :	310	. •	. •	: .,	.::		
gac	atg	tac	ccc	ac <b>c</b>	cgg	ggc	gtg	ggc	tat	gag	acc	atc	ctg	aaa	gag		11,31
Asp	Met	Tyr	Pro	Thr	Arg	Gly	Val	Gly	Tyr	Glu	Thr	Ile	Leu	Lys	Glu	:	
315	·Ţ	<i>:</i> .		,	320			9		325		·* :		•	330	•	
cag	aag	ggt	cag	agc	atg	ttc	gtg	gag	aac	aag	gcc	ttt	tcc	atg	gat		1179
Gln	Lys	Gly	G1n	Ser	Met	Phe	Val	Glu	Asn	Lys	Ala	Phe	Ser	Меt	Asp	•	
	•			335				•	340		•		-	345	- ÷		
gag	ccg	gtt	gca	gct	aag	agg	ccg	gtg	tca	сса	tac	agc	ggg	tac	aat		1227
Glu	Pro	Val	Ala	Ala	Lys	Arg	Pro	Val	Ser	Pro	Tyr	Ser	Gly	Tyr	Asn	•	
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Gly	Gln	Leu	Leu	Thr	Ser	Val	Tyr	Gln	Pro	Thr	Glu	Met	Ala	Leu	Met		
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His	Lys	Val	Pro	Ser	Glu	Gly	Ala	Tyr	Asp	Ile	Ile	Leu	Pro	Arg	Ala		
	380	٠	. •			385		•	• •		390		٠	٠		ē.	•
acc	gcc	aac	agc	cag	gtg	atg	ggc	agt	gcc	aac	tcg	acc	ctg	cgg	gct		1371
Thr	Ala	Asn	Ser	Gln	Val	Met	Gly	Ser	Ala	Asn	Ser	Thr	Leu	Arg	Ala		
395	1.		٠	·	400					405				, (	410		
gaa	gac	atg	tac	tcg	gcc	cag	agc	cac	cag	gcg	gcc	aca	ccg	ccg	aaa		1419
Glu	Asp	Met	Tyr	Ser	Ala	Gln	Ser	His	Gln	Ala	Ala	Thr	Pro	Prò	Lys	•	
	٠.	101	•	415		81		.:	420			•	+ 25	425	. •), '		
gac	ggc	aag	aac	tct	cag	gtc	tti	aga	aac	ccc	tac	gtg	tgg	gac			1464
Asp	Gly	Lys	Asn	Ser	Gln	Val	Phe	Λrg	Asn	Pro	Tyr	Väl	Trp	Asp	+:74		

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		Met Ala	•
ng tre tree tree tree		1	•
gct gcc gtc ccg aag agg atg agg	ggg cca gca	caa gcg aaa ctg ctg	103
Ala Ala Val Pro Lys Arg Met Arg	Gly Pro Ala	Gln Ala Lys Leu Leu	
5 3 5 7 1 1 10 10		415	
ccc ggg tcg gcc atc caa gcc ctt	gtg ggg ttg	gcg cgg ccg ctg gtc	151
Pro Gly Ser Ala Ile Gln Ala Leu	Val Gly Leu	Ala Arg Pro Leu Val	

RNSDOCID-VWO 011266042 LS

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ttg	gcg	ctc	ctg	ctt	gtg	tcc	gcc	gct	cta	tcc	agt	gtt	gta	tca	cgg'		199
Leu	Ala	Leu	Leu	Leu	Val	Ser	Ala	Ala	Leu	Ser	Ser	Val	Val	Ser	Arg		
35		٠.	•	•(•,	40					45		• 4	.:		50		
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Thr	Asp	Ser	Pro	Ser	Pro	Thr	Val	Leu	Asn	Ser	His	Ile	Ser	Thr	Pro		
				55					60		:			65			
aat	gtg	aat	gct	tta	aca	cat	gaa	aac	caa	acc	aaa	cct	tct	att	tcċ		295
Asn	Val	Asn	Ala	Leu	Thr	His	Glu	Asn	Gln	Thr	Lys	Pro	Ser	He	Ser		
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caa	atc	agc	acc	acc	ctc	cct	ccc	acg	acg	agt	acc	aag	aaa	agt	gga		343
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• • • • • • • • • • • • • • • • • • • •		85					90					95		٠.			
<i>aa</i> 2	<i>a</i> 02		at a	ate	cct	cat		tea	cct	act	cct			caa	σασ		391
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Giy		sei	Vai	vaı	F10		FIO	261	110	1111							
	100					105					110						420
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G]u	Ala	Asp	Asn	Asn	Glu	Asp	Pro	Ser	He		Glu	Glu	Asp	Leu			•
115	•				120					125					130		
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Met	Leu	Asn	Ser	Ser	Pro	Ser	Thr	Ala	Lys	Asp	Thr	Leu	Asp	Asn	Gly		
	,·. ,	•		135	• *	٠.,		÷	140	• • •	• .•	• ;	PI T	145		•	
gat	tat	gga	gaa	cca	gac	tat	gac	tgg	acc	acg	ggc	ccc	agg	gac	gac		535
Asp	Tyr	Gl∙y	Glu	Pro	Asp	Tyr	Asp	Trp	Thr	Thr	Gly	Pro	Arg	Asp <sup>°</sup>	Asp'	٠.	
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Asp	Glu	Ser	Asp	Asp	Thr	Leu	Glu	Glu	Asn	Arg	Gly	Tyr	Met	Glu	Ile	
	Ē	165					170					175		:		
gaa	cag	tca	gtg	aaa	tct	ttt	aag	atg	cca	tcc	tca	aat	ata	gaa	gag	631
Glu	Gln	Ser	Val	Lys	Ser	Phe	Lys	Met	Pro	Ser	Ser	Asn	Ile	Glu	Glu	
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Glu	Asp	Ser	llis	Phe	Phe	Phe	llis	Leu	Ile	Ile	Phe	Ala	Phe	Cys	Ile	
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Ala	Val	Val	Tyr	Ile	Thr	Tyr	His	Asn	Lys	Arg	Lys	Ile	Phe	Leu	Leu	
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gtt	caa	agc	agg	aaa	tgg	cgt	gat	ggc	ctt	tgt	tcc	aaa	aca	gtg	gaa	775
Va]	Gln	Ser	Arg	Lys	Trp	Arg	Asp	Gly	Leu	Cys	Ser	Lys	Thr	Val	Glu	
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Tyr	His	Arg	Leu	Asp	Gln	Asn	Val	Asn	Glu	Ala	Met	Pro	Ser	Leu	Lys	
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atgi	lgagi	tta a	aacat	taco	et <b>t</b> a	atati	ttaca	a cta	zttas	gttt	ttai	ttgt	ttt	agati	ttatta .	1110

ENSULUTION - MUSERNAS I -

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## 240/307

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Met Ala	1
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Met Ala  l  ggg tcg ccg ctg ctc tgg ggg ccg cgg ggc ggc	attg 103 Leu
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Ala	Glu	Thr	Gly	Ala	Pro	Arg	Arg	Phe	Arg	Arg	Ser	Val	Pro	Arg	Gly		
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gag	gcg	gcg	ggg	gcg	gtg	cag	gag	ctg	gcg	cgg	gcg	ctg	gcg	cat	ctg		295
Glu	Ala	Ala	Gly	Ala	Val	Gln	Glu	Leu	Ala	Arg	Ala	Leu	Ala	His	Leu		
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ctg	gag	gcc	gaa	cgt	cag	gag	cgg	gcg	cgg	gcc	gag	gcg	cag	gag	gct		343
Leu	Glu	Ala	Glu	Arg	Gln	Glu	Arg	Ala	Arg	Ala	Glu	Ala	Gln	Glu	Ala		
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Ala	Pro	Arg	Asn	Ser	Asp	Pro	Ala	Leu	Gly	Leu	Asp	Asp	Asp	Pro	Asp		
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Ala	Pro	Ala	Ala	Gln	Leu	Ala	Arg	Ala	Leu	Leu	Arg	Ala	Arg	Leu	Asp		
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gat	gct	gag	gag	gca	ggc	gac	gag	aca	ccc	gac	gtg	gac	ccc	gag	ctg	•	631
Asp	Ala	G1ú	Glu	Ala	G1y	Asp	Glu	Thr	Pro	Asp	Val	Asp	Pro	Glu	Leu	7.	
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Leu	Arg	Tyr	Leu	Leu	Gly	Arg	Ile	Leu	Ala	Gly	Ser	Ala	Asp	Ser	Glu		
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Gly	Val	Ala	Ala	Pro	Arg	Arg	Leu	Arg	Arg	Ala	Ala	Asp	His	Asp	Val		
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Gly	Ser	Glu	Leu	Pro	Pro	Glu	Gly	Val	Leu	Gly	Ala	Leu	Leu	Arg	Val		
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aaa	cgc	cta	gag	acc	ccg	gcg	ccc	cag	gtg	cct	gca	cgc	cgc	ctc	ttg		823
Lys	Arg	Leu	Glu	Thr	Pro	Ala	Pro	Gln	Val	Pro	Ala	Arg	Arg	Leu	Leu		
	··•	245					250					255	٠.,	•	€ '		
cca	ccc	t g	agca	ctgc	c cg	gatc	ccgt	gca	ccct	ggg	accc	agaa.	gt g	cccc	cgcca		880
Pro	Pro	٠.						,							• /		
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tcc	cgcc	acc	agga	ctgc	tc c	ccgc	cagc	a cg	tcca	gagc	aac	ttac	ccc	ggcc	agcca	g	940
ccc	tctc	acc	cgag	gatc	cc t	accc	cctg	g cc	ccac	aata	aac	atga	tct	gaag	cagc	• ?	998
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The services the services

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Gly	Ala	Ala	Arg	Leu	Pro	Ser	Arg	Val	Ala	Arg	Leu	Leu	Ser	Ala	Leu
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Phe	Tyr	Gly	Thr	Cys	Ser	Phe	Leu	Ile	Val	Leu	Val	Asn	Lys	Ala	Leu
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He	His	Phe	Pro	Asp	Phe	Лsp	Lys	Lys	Ile	Pro	Val	Lys	Leu	Phe	Pro
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Leu	Pro	Leu	Leu	Tyr	Val	Gly	Asn	His	lle	Ser	Gly	Leu	Ser	Ser	Thr
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Ser	Lys	Leu	Ser	Leu	Pro	Met	Phe	Thr	Val	Leu	Arg	Lys	Phe	Thr	Ile
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Pro	Leu	Thr	Leu	Leu	Leu	Glu	Thr	Ile	Ile	Leu	Gly	Lys	Gln	Tyr	Ser
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Leu	Asn	lle	Ile	Leu	Ser	Val	Phe	Ala	Ile	Ile	Leu	Gly	Ala	Phe	Ile
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Ala	Ala	Gly	Ser	Asp	Leu	Λla	Phe	Asn	Leu	Glu	Gly	Tyr	Ile	Phe	Va,1
				165					170				!	175	٠.,
Phe	Leu	Asn	Asp	Ile	Phe	Thr	Ala	Λla	Asn	Gly	Val	Tyr	Thr	Lys	Ģln
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Lys	Met	Asp	Pro	Lys	Glu	Leu	Gly	Lys	Tyr	Gly	Val	Leu	Phe	Tyr	Asn
		195	1			,	200		7			205		••	•
Λla	Cys	Phe	Met	Ile	Ile	Pro	Thr	Leu	lle	Ile	Ser	Val	Ser	Thr	Gly
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Asp	Leu	Gln	Gln	Ala	Thr	Glu	Phe	Asn	Gln	Trp	Lys	Asn	Val	Val	Phe
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Ile	Leu	Gln	Phe	Leu	Leu	Ser	Cys	Phe	Leu	Gly	Phe	Leu	Leu	Met	Tyr
	1 .,			245			٠.		250	•				255	
Ser	Thr	Val	Leu	Cys	Ser	Tyr	Tyr	Asn	Ser	Ala	Leu	Thr	Thr	Ala	Val
			260		•			265					270		
Val	Gly	Ala	Ile	Lys	Asn	Val	Ser	Val	Ala	Tyr	Ile	Gly	Ile	Leu	Ile
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Gly	Gly	Asp	Tyr	Ile	Phe	Ser	Leu	Leu	Asn	Phe	Val	Gly	Leu	Asn	Ile
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Cys	Met	Ala	Gly	Gly	Leu	Arg	Tyr	Ser	Phe	Leu	Thr	Leu	Ser	Ser	Gln
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		10.4		325					330					335	56 I
Ser															; .;
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Arg	Pro	Leu	Phe	Ala	Gly	Leu	Ser	Asp	Ile	Ser	Ile	Ser	Gln	Asp	Ile
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Pro	Val	Glu	Gly	Glu	Ile	Thr	Ile	Pro	Жet	Arg	Ser	Arg	Ile	Arg	Glu
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Phe	Asp	Ser	Ser	Thr	Leu	Asn	Glu	Ser	Val	Arg	Asn	Thr	Ile	Met	Arg
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Lys	Ser	Asn	Thr	Leu	Leu	Arg	Asp	Trp	Asp	Leu	Trp	Gly	Pro	Leu	Ile
				85					90					95	
Leu	Cys	Val	Thr	Leu	Ala	Leu	Met	Leu	Gln	Arg	Asp	Ser	Ala	Asp	Ser
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Glu	Lys	Asp	Gly	Gly	Pro	Gln	Phe	Ala	Glu	Val	Phe	Val	Ile	Val	Trp
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	130					135					140				
lle	Ser	Phe	Phe	Gln	Ser	Leu	Cys	Val	Leu	Gly	Tyr	Cys	Ile	Leu	Pro
145					150					155		•			160
Leu	Thr	Val	Ala	Met	Leu	He	Cys	Arg	Leu	Val	Leu	Leu	Ala	Asp	Pro :
	٠.	* •		165					170					175	
Gly	Pro	Val	Asn	Phe	Met	Val	Arg	Leu	Phe	Val	Val	Ile	Val	Met	Phe
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Ala Trp Ser	Ile	Val	Ala	Ser	Thr	Ala	Phe	Leu	Λla	Asp	Ser	Gln	Pro	
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Pro Asn Arg	Arg	Ala	Leu	Ala	Val	Tyr	Pro	Val	Phe	Leu	Phe	Tyr	Phe	
210		٠	. •	215					220		• •	٠	••:	:
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Asp Pro Glu	Pro	Glu	Ser	Pro	Pro	Ala	Pro	Gly	Arg	Gly	Pro	Ala	Gly	
• •	20	ř	•	t		25		ē .	. 8	٠,	30	· .		90.
Ser Pro Ala	His	Leu	His	Thr	Gly	Thr	Phe	Trp	Leu	Thr	Arg	Ile	Val	
35					40		• •			45		•	ņ:·	٠
Leu Leu Lys	Ala	Leu	Ala	Phe	Val	Tyr	Phe	Val	Ala	Phe	Leu	Val	Ala	
50	٠.	• .	-	55	•			,	60	٠,	•	٠.	13.5	* (
Phe His Gln	Asn	Lys	Gln	Leu	Ile	Gly	Asp	Arg	Gly	Leu	Leu	Pro	Cys	`•
65	٠.	16.4	70	٠.	. •		٠.	75	. •	٠.	٠, ٠	: .47	<sup>1</sup> 80	, , ,
Arg Val Phe	Leu	Lys	Asn	Phe	Gln	Gln	Tyr	Phe	Gln	Asp	Arg	Thr	Ser	
£ (1 1 1)	: '	85	. •	r *,	٠,٠	• • •	. 90		3	***		95	or'	, <b>'</b> ·
Trp Glu Val	Phe	Ser	Tyr	Met	Pro	Thr	Ile	Leu	Trp	Leu	Met	Λsp	Trp	

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Trp	Tyr	Ser	Phe	Gly	Trp	Glu	Ser	Gln	Leu	Leu	Glu	Thr	Gly	Phe	Leu	
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Gly	Ile	Phe	Leu	Cys	Pro	Leu	Trp	Thr	Leu	Ser	Arg	Leu	Pro	G1n	His	
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Thr	Pro	Thr	Ser	Arg	Ile	Val	Leu	Trp	Gly	Phe	Arg	Trp	Leu	Ile	Phe	
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Pro	Asn	Pro	Val	Ala	Tyr	Tyr	Leu	His	His	Ser	Pro	Trp	Trp	Phe	His	
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Phe	Leu	Phe	Leu	Gly	Arg	Arg	Ala	Cys	Ile	Ile	His	Gly	Val	Leu	Gln	
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Gln	Pro	Leu	He	Thr	Leu	Gln	Tyr	Phe	Ser	Leu	Glu	Ile	Leu	Val	Ile	
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Ser	Phe	Leu	Leu	Leu	Leu	Ala	Val	Leu	Ile	Ala	Thr	Tyr	Tyr	Val	Glu	
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Gly	Val	His	Gln	Gln	Tyr	Val	G1n	Arg	Ile	Glu	Lys	Gln	Phe	Leu	Leu
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Val	Thr	Leu	۸la	Ala	Tyr	Glu	Cys	Asn	Ser	Val	Asn	Phe	Pro	Glu	Pro
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Pro	Tyr	Pro	Asp	Gln	Ile	Ile	Cys	Pro	Λsp	Glu	Glu	Gly	Thr	G1u	Gly
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Ala	Ser	Arg	Ala	Lys	Ļeu	Ala	Val	Gln	Lys	Leu	Val	Gln	Lys		
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Phe	Phe	Gly	Ile	Leu	Ala	Cys	Ala	Ser	Ile	Pro	Asn	Pro	Leu	Phe	Asp
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Leu															Phe
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Pho	Glv	Ala	Thr	Leu	He	Glv	Livs	Ala	He	He	Lys	Met	His	Ile	Gln

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1															. ·.	
Thr C	iln <i>i</i>	Ala '	Val :	Ser	Lys										Val	
	:														2 I 22	

			_	_	٠.			<b>T</b> 1	n	C-	4.1	C1	C1	A 1 -	V = 1	
Ala				Ser												
	: L ·	··35	1			• •	· 40	•	•	• 1	ě	· 45	••	• •	3 +	• •
Glu	Phe	Pro	Ala	Asp	Lys	Met	Val	Ser	Val	Leu	Val	Gln	Glu	Gly	His	
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Ser	Gly	Ala	G1 y	Phe	Gly	Val	Ser	Asp	Val	Gly	Ser	His	Leu	Asp	Cys	
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Gly	Ala	Gly	Glu	Pro	Ala	Val	Phe	Arg	Asp	Ser	Asp	Arg	Phe	Ser	Trp	
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His	Asp	Pro	His	Leu	Trp	Arg	Ser	Gly	Asp	Glu	Ala	Pro	Gly	Leu	Phe	
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Phe	Val	Asp	Ala	Glu	Arg	Val	Pro	Cys	Arg	His	Аsp	Asp	Val	Phe	Phe	
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Pro	Pro	Ser	Ala	Ser	Phe	Arg	Val	Gly	Leu	Gly	Pro	Gly	Ala	Ser	Pro	
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His	Gly	Pro	Gly	Ala	Leu	Ser	Val	Gly	Pro	Glu	Asp	Cys	Ala	Asp	Pro	
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Ala				Pro												

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Ala	Asp	Ser	Thr	Ser	His	Ser	Tyr	Phe	Val	Asn	Pro	Leu	Phe	Ala	Gly	•
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Leu	Val	Leu	Pro	Val	Val	Glu	Ala	Val	Glu	Ala	Gly	Asp	Ala	lle	Ala	
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Leu	Leu	ı Leu	Gly	Val	Val	Leu	Ser	Ile	Thr	Gly	Ile	Cys	Ala	Cys	Leu	
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Met	A1:	a Leu	Pró	Gln	Met	Cvs	Asp	Glv	Ser	His	l.eu	Ala	Ser	Thr	Leu	

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Arg	Tyr	Cys	Met	Thr	· Val	Ser	Gly	Thr	Val	Val	Leu	Val	Ala	Gly	Thr
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Leu	Cys	Phe	Ala	Trp	Trp	Ser	Glu	G1 y	Asp	Ala	Thr	Ala	Gln	Pro	Gly
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Leu	Leu	lle	Gly	Leu	Leu	Trp	Ser	Val	Lys	Ala	Ser	Ile	Pro	Gly	Pro
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Ser	Arg	Asp	Ala	Leu	Leu	Ser	Thr	Gln	Pro	Ala	Trp	Pro	Pro	Pro	Ser
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Tyr	Glu	Ser	Ile	Ser	Leu	Ala	Leu	Asp	Ala	Val	Ser	Ala	Glu	Thr	Thr
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Leu	Leu	Ser	Tyr	Asp	Leu	Phe	Val	Asn	Ser	Phe	Ser	Glu	Leu	Leu	Gln
			20					25					30		
Lys	Thr	Pro	Val	Ile	Gln	Leu	Val	Leu	Phe	Ile	Ile	Gln	Asp	Ile	Ala
		35					40					45			
Val	Leu	Phe	Asn	Ile	Ile	Ile	Ile	Phe	Leu	Met	Phe	Phe	Asn	Thr	Phe
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Thr	Ile	Ile	Leu	Thr	Ala	Val	Tyr	Phe	Ala	Leu	Ser	Ile	Ser	Leu	His .
	,			85		e			90					95	•
Val	Trp	Val	Met	Asn	Leu	Arg	Trp	Lys	Asn	Ser	Asn	Ser	Phe	Ile	Trp
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ENSULUTION NITSERNAS 1 -

Thr Asp Gly Leu Gln Met Leu Phe Val Phe Gln Arg Leu Ala Ala Val 120 125 Leu Tyr Cys Tyr Phe Tyr Lys Arg Thr Ala Val Arg Leu Gly Asp Pro 140 135 130 His Phe Tyr Gln Asp Ser Leu Trp Leu Arg Lys Glu Phe Met Gln Val 155 160 150 145 Arg Arg <210> 130 <211> 221 <212> PRT <213> Homo sapiens <400> 130 Met Ala Leu Ala Leu Ala Ala Leu Ala Ala Val Glu Pro Ala Cys Gly 🦠 🕒 1 5 10 15 Ser Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly Glu Pro Glu 25 30 · Gln Ala Ala Gly Asp Ala Pro Pro Pro Tyr Ser Ser Ile Ser Ala Glu 40 45 35 Ser Ala Ala Tyr Phe Asp Tyr Lys Asp Glu Ser Gly Phe Pro Lys Pro 50 55 60 Pro Ser Tyr Asn Val Ala Thr Thr Leu Pro Ser Tyr Asp Glu Ala Glu 80 65 70 75 Arg Thr Lys Ala Glu Ala Thr Ile Pro Leu Val Pro Gly Arg Asp Glu 90 ··· 85

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<211> 1218

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<400> 134

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Ala Gly Gly Glu Pro Gly Ala Ala Arg Leu Pro Ser Arg Val Ala Arg	*
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7	hr	Leu	Ser	Ser	Gln	Leu	Lys	Pro	Lys	Pro	Val	Gly	Glu	Glu	Asn	Ile		
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t	gt	ttg	gat	ttg	aag	agc	ta	aaga	gtct	gc a	gcag	gatt	g ga	gact	gact			1120
C	ys	Leu	Asp	Leu	Lys	Ser		÷ .	ř	. •	٠			. •	,	•••	٠٠.	
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135	٠	.:	•	• •	140	٠.				145		٠		i,	150	
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Ala	Val	Tyr	Pro	Val	Phe	Leu	Phe	Tyr	Phe	Val	Ile	Ser	Trp	Met	Ile		
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Leu	Thr	Phe	Thr	Pro	Gln												
	•	· -		235						*				2			
aago	acat	ct g	gaaag	atgo	aat	tcac	cate	gag	cttt	gtc	tctg	gcco	ett a	atttg	tcta	<b>a</b> .	840
tttt	ggag	gt a	atttg	ataa	c tg	agta	ggtg	agg	agat	taa	aagg	gago	ca i	tatag	cact	g	900
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ttaa	acad	at t	gcct	tate	a ct	atta	gaat	atg	ccto	tct	tttc	ataa	at a	aaaaa	tacat	t !	200
ggto	tata	tc c	attt	tctt	t ta	tttc	tctc	tct	taag	ctt	aaaa	aggc	aa t	tgaga	gaggi	t l	260
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BNSDOCID: <WO 0112660A2 L >

Later Service Statement

## 284/307

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1 5 10
egg aag act ggg tac teg gat eeg gag eet gag teg eeg eeg eeg eeg 9
Arg Lys Thr Gly Tyr Ser Asp Pro Glu Pro Glu Ser Pro Pro Ala Pro
15 20 25
ggg cgt ggc ccc gca ggc tct ccg gcc cat ctc cac acg ggc acc ttc 14
Gly Arg Gly Pro Ala Gly Ser Pro Ala His Leu His Thr Gly Thr Phe
30 35 40
tgg ctg acc cgg atc gtg ctc ctg aag gcc cta gcc ttc gtg tac ttc 19
Trp Leu Thr Arg Ilc Val Leu Leu Lys Ala Leu Ala Phe Val Tyr Phe
45 50
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Val Ala Phe Leu Val Ala Phe His Gln Asn Lys Gln Leu Ile Gly Asp
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Arg Gly Leu Leu Pro Cys Arg Val Phe Leu Lys Asn Phe Gln Gln Tyr
75 80 85 90 .
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Phe Gln Asp Arg Thr Ser Trp Glu Val Phc Ser Tyr Met Pro Thr Ile
Sec. 105

ctc	tgg	ctg	atg	gac	tgg	tca	gac	atg	aac	tcc	aac	ctg	gac	ttg	ctg'	•	386
Leu	Trp	Leu	Met	Asp	Trp	Ser	Asp	Met	Asn	Ser	Asn	Leu	Asp	Leu	Leu	•	
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gct	ctt	ctc	gga	ctg	ggc	atc	tcg	tct	ttc	gta	ctg	atc	acg	ggc	tgc '		434
Ala	Leu	Leu	Gly	Leù	Gly	Ile	Ser	Ser	Phe	Val	Leu	Ile	Thr	Gly	Cys	.•	
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gcc	aac	atg	ctt	çtc	atg	gct	gcc	ctg	tgg	ggc	ctc	tac	atg	tcc	ctg		482
۸la	Asn	Met	Leu	Leu	Met	Ala	Ala	Leu	Trp	Glý	Leu	Tyr	Met	Ser	Leu	· ·	
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gtt	aat	gtg	ggc	cat	gtc	tgg	tac	tct	ttc	gga	tgg	gag	tcc <sup>.</sup>	cag	ctt		530
Val	۸sn	Val	Gly	His	Val	Trp	Tyr	Ser	Phe	Gly	Trp	Glu	Ser	Gln	Leu		
155	٠.				160				,	165				ı	170		
ctg	gag	acg	ggg	ttc	ctg	ggg	atc	ttc	ctg	tgc	cct	ctg	tgg	acg	ctg		578
Leu	Glu	Thr	Gly	Phe	Leu	Gly	Ile	Phe	Leu	Cys	Pro	Leu	Trp	Thr	Leu		
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Ser	Arg	Leu	Pro	Gln	His	Thr	Pro	Thr	Ser	Arg	Ile	Val	Leu	Trp	Gly.	• •	
	10 <b>1</b>		190		٠.			195				٠.	200	:	· .		
ttc	cgg	tgg	ctg	atc	ttc	agg	atc	atg	ctt	gga	gca	ggc	ctg	atc	aag		674
Phe	Arg	Trp	Leu	Ile	Phe	Arg	Ile	Met	Leu	Gly	Ala	Gly	Leu	Ile	Lys	•-	
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ile	Arg	Gly	Asp	Arg	Cys	Trp	Arg	Asp	Leu	Thr	Cys	Met	Asp	Phe	His	:	
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tat	gag	acc	cag	CCS	atg	ccc	aat	cct	gtg	gca	tac	tac	ctg	cac	cac		770

ıyr	GIU	ınr	GIN	Pro	Met	Pro	Asn	Pro	Vai	Ala	lyr	lyr	Leu	HIS	HIS	
235	• •	.*	,	٠.	240	-			• .	245					250	
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Glu	Leu	Leu	Val	Pro	Phe	Phe	Leu	Phe	Leu	Gly	Arg	Arg	Ala	Cys	Ile	
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Ile	His	Gly	Val	Leu	Gln	Ile	Leu	Phe	<b>G</b> ln	Ala	Val	Leu	lle	Val	Ser	
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Cys	Phe	Asp	Asp	Ala	Thr	Leu	Gly	Phe	Leu	Phe	Pro	Ser	Gly	Pro	Gly	
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Ser	Leu	Lys	Asp	Arg	Val	Leu	Gln	Met	Gln	Arg	Asp	Iļe	Arg	Gly	Ala	
	· •	•		335					340					345	+ + 1 <b>+</b>	
cgg	ссс	gag	ccc	aga	ttc	ggc	tcc	gtg	gtg	cgg	cgt	gca	gcc	aac	gtc	1106
Arg	Pro	Glu	Pro	Arg	Phe	Gly	Ser	Val	Val	Arg	Arg	Ala	Ala	Asn	Val	
	.· ·	,	350		•	**		355	. •		r		360	•		
tcg	ctg	ggc	gtc	ctg	ctg	gcc	tgg	ctc	agc	gtg	ссс	gtg	gtc	ctc	aac	1154
Ser	Leu	Glv	Val	Leu	Leu	Ala	Trn	Leu	Ser	Val	Pro	Val	Val	l.eu	Asn	

	•	365		٠.		٠.	370		•			375	12		٠.,٠	ė	
ttg	ctg	agc	tcc	agg	cag	gtc	atg	aac	acc	cac	ttc <sub>.</sub>	aac	tct	ctt	cac	•	1202
Leu	Leu	Ser	Ser	Arg	G1n	Val	Met	Asn	Thr	His	Phe	Asn	Ser	Leu	His		
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atc	gtc	aac	act	tac	ggg	gcc	ttc	gga	agc	atc	acc	aag	gag	cgg	gcg		1250
Ile	Val	Asn	Thr	Tyr	Gly	Ala	Phe	Gly	Ser	lle	Thr	Lys	Glu	Arġ	Ala		
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Glu	Val	Ile	Leu	Gln	Gly	Thr	Ala	Ser	Ser	Asn	Ala	Ser	Ala	Pro	Asp		
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gcc	atg	tgg	gag	gac	tac	gag	ttc	aag	tgc	aag	cca	ggt	gac	ccc	agc		1346
Ala	Met	Trp	G]lu	Asp	Tyr	Glu	Phe	Lys	Cys	Lys	Pro	Gly	Asp	Pro	Ser	-	
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aga	cgg	ccc	tgc	ctc	atc	tcc	ccg	tac	cac	tac	cgc	ctg	gac	tgg	ctg		1394
Arg	Arg	Pro	Cys	Leu	Ile	Ser	Pro	Tyr	His	Tyr	Arg	Leu	Λsp	Trp	Leu	•	•
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atg	tgg	ttc	gcg	gcc	ttc	cag	acc	tac	gag	cac	aac	gac	tgg	atc	atc		1442
Met	Trp	Phe	Ala	Ala	Phe	Gln	Thr	Tyr	Glu	His	Asn	Asp	Trp	lle	Ile		
	460					465					470	+ .		. •	Fres *		
cac	ctg	gct	ggc	aag	ctc	ctg	gcc	agc	gac	gcc	gag	gcc	ttg	tcc	ctg		1490
His	Leu	Ala	Gly	Lys	Leu	Leu	Ala	Ser	Asp	Ala	Glu	Ala	Leu	Ser	Leu		
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Leu	Ala	His	Asn	Pro	Phe	Ala	Gly	Arg	Pro	Pro	Pro	Arg	Trp	Val	Arg	٠,٠	
	7:. ,	٠	•	195			. • •		500	. •	· (•	<u>:</u> ·	•1	505	*}:+	· ·	

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Gly Glu His Tyr Arg Tyr Lys Phe Ser Arg Pro Gly Gly Arg His Ala	
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gcc gag ggc aag tgg tgg gtg cgg aag agg atc gga gcc tac ttc cct 1634	
Ala Glu Gly Lys Trp Trp Val Arg Lys Arg Ile Gly Ala Tyr Phe Pro	
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ccg ctc agc ctg gag gag ctg agg ccc tac ttc agg gac cgt ggg tgg 1682	
Pro Leu Ser Leu Glu Glu Leu Arg Pro Tyr Phe Arg Asp Arg Gly Trp	
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Met Ala Glu	

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Asn	Gly	Lys	Asn	Cys	Asp	Gln	Arg	Arg	Val	۸la	Met	Asn	Lys	Glu	His		
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His	Asn	Gly	Asn	Phe	Thr	Asp	Pro	Ser	Ser	Val	Asn	Glu	Lys	Lys	Arg		
20	<i>i</i> •	·			25			•		30					35		
agg	gag	cgg	gaa	gaa	agg	cag	aat	att	gtc	ctg	tgg	aga	cag	ccg	ctc		259
Arg	Glu	Arg	Glu	Glu	Arg	Gln	Asn	Ile	Val	Leu	Trp	Arg	Gln	Pro	Leu		
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att	acc	ttg	cag	tat	ttt	tct	ctg	gaa	atc	ctt	gta	atc	ttg	aag	gaa		307
Ile	Thr	Leu	G1n	Tyr	Phe	Ser	Leu	Glu	Ile	Leu	Val	Ile	Leu	Lys	Glu		
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Trp	Thr	Ser	Lys	Leu	Trp	His	Arg	Gln	Ser	Ile	Val	Val	Ser	Phe	Leu	•	
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Gln	Gln	Tyr	Val	Gln	Arg	Ile	Glu	Lys	Gln	Phe	Leu	Leu	Tyr	Ala	Tyr		
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Ile	Gly	Thr	Ala	Ile	Gly	Glu	Leu	Pro	Pro	Tyr	Phe	Met	Ala	۸rg	Ala	
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Ala	Arg	Leu	Ser	Gly	Ala	Glu	Pro	Asp	Asp	Glu	G1u	Tyr	Gln	Glu	Phe	
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Glu	Glu	Met	Leu	Glu	His	Ala	Glu	Ser	Ala	Gln	Λsp	Phe	Ala	Ser	Arg	
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gcc	aaa	ctg	gca	ġtt	caa	aaa	cta	gta	cag	aaa	gtt	gga	ttt	ttt	gga	883
Ala	Lys	Leu	Ala	Val	Gln	Lys	Leu	Val	Gln	Lys	Val	Gly	Phe	Phe	Gly	
	245		. •	: 8	i,	250	•	,-		- ,	255			. ~	· (1)	
att	ttg	RCC	tet	gct	tca	att	cca	aat	cct	tta	ttt	gat	ctg	gct	gga	931

	Ile	Leu	Ala	Cys	Ala	Ser	Ile	Pro	Asn	Pro	Leu	Phe	Asp	Leu	Ala	Gly		
	260				٠	265	•			•	270		i	* 1	•	275	. :	
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,	Ile	Thr	Cys	Gly	His	Phe	Leu	Val	Pro	Phe	Trp	Thr	Phe	Phe	Gly	Ala		
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	Thr	Leu	Ile	Gly	Lys	Ala	Ile	Ile	Lys	Met	His	Ile	Gln	Lys	Ile	Phe		
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	Val	Ile	Ile	Thr	Phe	Ser	Lys	His	Ile	Val	Glu	Gln	Met	Val	Ala	Phe		
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	Ile	Gly	Ala	Val	Pro	Gly	Ile	Gly	Pro	Ser	Leu	Gln	Lys	Pro	Phe	Gln		
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	Glu	Tyr	Leu	Glu	Ala	Gln	Arg	Gln	Lys	Leu	His	His	Lys	Ser	Glu	Met		
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	Gly	Thr	Pro	Gln	Gly	Glu	Asn	Trp	Leu	Ser	Trp	Met	Phe	Glu	Lys	Leu		
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	gtc	gtt	gtc	atg	gtg	tgt	tac	ttc	atc	cta	tct	atc	att	aac	tcc	atg		1267
	Val	Val	Val	Met	Val	Cys	Tyr	Phe	Ile	Leu	Ser	lle	Ile	Asn	Ser	Met		
		٠.	••	375		,	* * *		380	٠		٠.	*	385		•••		
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Lys Thr Lys				•	•
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	Thr	Pro	Cys	Ala	Gly	Gly	Ala	Val	Glu	Phe	Pro	Ala	Asp	Lys	Met	Val		
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Arg	Cys	Pro	Gln	Ala	Ala	Cys	His	Ser	Ala	Leu	Arg	Pro	Gln	Gly	Gln		
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Cys	Cys	Asp	Leu	Cys	Gly	Ala	Val	Val	Leu	Leu	Thr	His	Gly	Pro	Ala		
	250			<u>.</u> .		255		<b></b> -	<b>₹</b> · •	,	260			<b>~</b> :			

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Leu	Pro	Gln	Tyr	His	Gly	Leu	Gln	Val	Ala	Val	Ser	Lys	Val	Pro	Arg		
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Ser	Ser	Arg	Leu	Arg	Glu	Ala	Asp	Thr	Glu	Ile	Gln	Val	Val	Leu	Val		
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											Leu						
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Leu	Ala	Asp	Val	Ala	Glu	Asn	Gly	Glu	Ala	Leu	Gly	Val	Leu	Glu	Ala		
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Leu	Ala	Gly	Gly	Val	Ala	Ala	Ala	Val	Leu	Leu	Ala	Leu	Leu	Val	Leu'		
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Dea			380		Dea	Dea		385									
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agg	cac	gag	gcg	gcg	gcc	ccg	gct	gga	gcg	ccc	ctc	ggc	itc	cgc	aac		1204

BRIGHOUTH - MICH - 011266042 I

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Pro Val Phe Asp Val Thr Ala Ser Glu Glu Leu Pro Leu Pro Arg Arg	
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Leu Ser Leu Val Pro Lys Ala Ala Asp Ser Thr Ser His Scr Tyr	
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Phe Val Asn Pro Leu Phe Ala Gly Ala Glu Ala Glu Ala	
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Ser Leu Val Leu Met Ser Leu Leu Leu Val Leu Pro Val Val Glu'Ala	
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Val Glu Ala Gly Asp Ala Ile Ala Leu Leu Cly Val Val Leu Ser	
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Gly	Ser	His	Leu	Ala	Ser	Thr	Leu	Arg	Tyr	Cys	Met	Thr	Val	Ser	G1y	
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Thr	Val	Val	Leu	Val	Àla	Gly	Thr	Leu	Cys	Phe	Ala	Trp	Trp	Ser	Glu	
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Gly	Asp	Ala	Thr	Ala	Gln	Pro	Gly	Gln	Leu	Ala	Pro	Pro	Thr	Glu	Tyr	
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Pro	Val	Pro	Glu	Giv	Pro	Ser	Pro	Leu	Leu	Arg	Ser	Val	Ser	Phe	Val	

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Gly Asp Ala Gly Pro Glu Thr Ser Thr Ala	Val Glu Lys Lys Glu Lys
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Phe	Leu	Leu	Leu	Ser	Tyr	Asp	Leu	Phe	Val	Asn	Ser	Phe	Ser	Glu	Leu		
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ctc	caa	aag	act	cct	gtc	atc	cag	ctt	gtg	ctc	ttc	atc	atc	cag	gat		324
Leu	Gln	Lys	Thr	Pro	Val	Ile	Gln	Leu	Val	Leu	Phe	Ile	Ile	Gln	Asp		
	•	•		35			•	. •	40	•				45	•	,	•
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Ile	Ala	Val	Leu	Phe	Asn	Ile	Ile	Ile	Ile	Phe	Leu	Met	Phe	Phe	Asn		
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acc	ttc	gtc	ttc	cag	gct	ggc	ctg	gtc	aac	ctc	cta	ttc	cat	aag	ttc		420
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Lys	Gly	Thr	Ile	Ile	Leu	Thr	Ala	Val	Tyr	Phe	Ala	Leu	Ser	Ile	Ser		
	80					85					90					•	
ctt	cat	gtc	tgg	gtc	atg	aac	tta	cgc	tgg	aaa	aac	tcc	aac	agc	ttc		516
Leu	His	Val	Trp	Val	Met	Asn	Leu	Arg	Trp	Lys	Asn	Ser	Asn	Ser	Phe	•	
95					100					105					110		
ata	tgg	aca	gat	gga	ctt	caa	atg	ctg	ttt	gta	tţc	cag	aga	cta	gca	•	564
Ile	Trp	Thr	Asp	Gly	Leu	Gln	Met	Leu	Phe	Val	Phe	Gln	Arg	Leu	Ala	٠	
-				115					120					125	•		
gca	gtg	ttg	tac	tgc	tac	ttc	tat	aaa	cgg	aca	gcc	gta	aga	cta	ggc		612
Ala	Val	Leu	Tyr	Cys	Tyr	Phe	Tyr	Lys	Arg	Thr	Ala	·Val	Arg	Leu	Gly		
			130	)				135	•				140	)			
ant	- 00+		. ++0	tac	· cad	gar	. tct	tto	too	cte	cgc	aas	gas	tto	atg		660

400 1 12 84

180

#### 305/307

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Gin Val Arg Arg	
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eggeeteeca gegeteecaa geegeagegg eegegeeeet teagetaget egetegeteg

231		tg ·	gct	g go	g go	g tt	g go	gʻtt	g go	c at	gcgc	gg ct	gcc	ctgct	cc c	gctt	ctc
		eu į	a Le	a Al	eu Al	a Le	u Al	la Le	et Al	Ме			•				
:	:	* -	- "		5				1					9.			
279		aat	cag	ttg	cag	cag	tac	cgg	agc	ggc	tgc	gcc	ccg	gag	gtc	gcg	gcg
		Asn	Gln	Leu	Gln	Gln	Tyr	Arg	Ser	Gly	Cys	Ala	Pro	Glu	Val	Ala	Ala
			·.			20					15					10	
327		cca	cct	gct	gat	ggt	gca	gct	cag	gaa	cct	gaa	gga	tct	gag	gaa	gaa
		Pro	Pro	Ala	Asp	Gly	Ala	Ala	Gln	Glu	Pro	Glu	Gly	Ser	Glu	Glu	Glu
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	- 1				85					80					75		
519		ttt	gat	gat	cgg	ggt	gtg	ttt	gat	gag	gat	aga	ggg	cct	gtt	ttg	cct
	•	Phe	Asp	Asp	Arg	Gly	Val	Phe	Asp	Glu	Asp	Arg	Gly	Pro	Val	Leu	Pro
	•			•	٠	100					95					90	
567	•,	tta	atg	ttc	att	ggg	gat	aat	gga	ata	agg	ctg	cag	gac	gct	gat	gat
		Leu	Met	Phe	Ile	Gly	Asp	Asn	Gly	Ile	Arg	Leu	Gln	Asp	Ala	Asp	Asp
	I	120	٠.	•			115					110					105
615		tct	ctg	ttc	ttt	ggg	att	tgg	aac	ttt	ctc	ttc	gca	atg	ttc	ttt	act

هيتوا بديان

1112

Thr	Phe	Phe	Met	Ala	Phe	Leu	Phe	Asn	Trp	Ile	G1y	Phe	Phe	Leu	Ser	
				125					130			•		135		
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Phe	Gly	Leu	Ser	Leu	Ile	Lys	Trp	Ile	Leu	Ile	Val	Arg	Phe	Ser	Thr	•
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Tyr	Phe	Pro	Gly	Tyr	Phe	Asp	Gly	Gln	Tyr	Trp	Leu	Trp	Trp	Val	Phe	
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Lys	Val	Arg	Lys	Met	Pro	Glu	Thr	Phe	Ser	Asn	Leu	Pro	Arg	Thr	Arg	
				205					210		٠			215		
gtt	ctc	ttt	att	tat	taa	agat	gtt	ttct	ggca:	aa g	gcct	tcct	g ca	ttta	tgaa	910
Val	Leu	Phe	Ile	Tyr									·			
			220				-									
ttc	t <b>ct</b> c	tca	agaa	gcaa	ga g	aaca	cctg	c ag	gaag	tgaa	tca	agat	gca	gaac	acagag	970
gaa	taat	cac -	ctgc	ttta	aa a	aaat	aaag	t ac	tgtt	gaaa	ag				•	1012

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- (71) Applicants (for all designated States except US): SAGAMI CHEMICAL RESEARCH CENTER [JP/JP]; 4-1. Nishi-Ohnuma 4-chome, Sagamihara-shi, Kanagawa 229-0012 (JP). PROTEGENE INC. [JP/JP]; 2-20-3, Naka-cho, Meguro-ku, Tokyo 153-0065 (JP).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): KATO, Seishi [JP/JP]; 3-46-50, Wakamatsu, Sagamihara-shi, Kanagawa 229-0014 (JP). KIMURA, Tomoko [JP/JP]; 715, 2-9-1, Kohoku, Tsuchiura-shi, Ibaraki 300-0032 (JP).

- (74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).
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11/12660 A3

(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

(57) Abstract: The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells expressing these DNAs and antibodies directed to these proteins.

#### INTERNATIONAL SEARCH REPORT

International Application No PC1, JP 00/05356

والمراجا فيهداج A. CLASSIFICATION OF SUBJECT MATTER
1PC 7 C12N15/12 C12N1/21 C12N5/10 C07K14/47 - C07K16/18 According to International Patent Classification (IPC) or to both national classification and IPC Minimum documentation searched (classification system followed by classification symbols) C12N C07K IPC 7 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) STRAND, MEDLINE C. DOCUMENTS CONSIDERED TO BE RELEVANT Category \* Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. WO 99 13074 A (TSURITANI KATSUKI ;YAZAKI Х 1-7 MADOKA (JP); MATSUMOTO KAYO (JP); TAISHO) 18 March 1999 (1999-03-18) SEQ ID NO:1 is 100% identical to SEQ ID NO:1 of present application figure 5 X Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or other means ments, such combination being obvious to a person skilled in the art. document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 19 02 01 27 November 2000 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Herrmann, K Fax: (+31-70) 340-3016

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/JP 00/05356

Box I	Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This Inte	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2.	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	rnational Searching Authority found multiple inventions in this international application, as follows:
	see additional sheet
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
з	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. X	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  1 - 7 (all partially)
Remark	on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.
	•

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Invention 1: Claims 1-7 (all partially)

Polypeptide comprising an amino acid sequence as in SEQ ID NO:1 and subject-matter relating thereto. Polynucleotides encoding the polypeptide of SEQ ID NO:1 such as a polynucleotide comprising a polynucleotide sequence as in SEQ ID NO:11 (coding sequence) or a polynucleotide consisting of a polynucleotide sequence as in SEQ ID NO: 21 (complete cDNA sequence) and subject-matter relating thereto.

2. Claims: Invention 2-50: Claims 1-7 (all partially)

Idem as subject 1 but limited to each of the polypeptides as in SEQ ID NOs:2-10, 31-40, 61-70, 91-100 and 121-130 and polynucleotides as in SEQ ID NOs:12-20, 41-50, 71-80, 101-110, 131-140 and SEQ ID NOs:22-30, 51-60, 81-90, 111-120 and 141-150, respectively. Invention 2 is limited to subject-matter relating to SEQ ID NOs:2 (protein), 12 (coding sequence) and 22 (complete cDNA), invention 3 to SEQ ID NOs 3, 13 and 23, etc.



ormation on patent family members

PC1/JP 00/05356

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9913074 A	18-03-1999	AU 8999298 A JP 11151096 A	29-03-1999 08-06-1999

Form PCT/ISA/210 (patent family ennex) (July 1992)